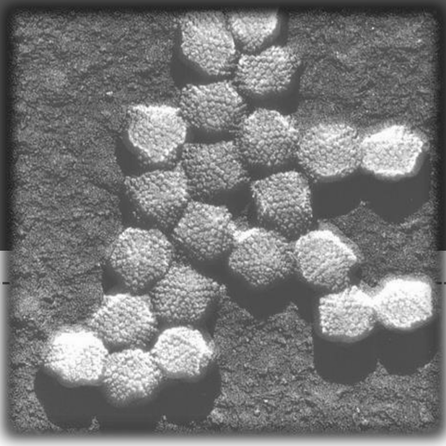
Respiratory Threats in the Tropics

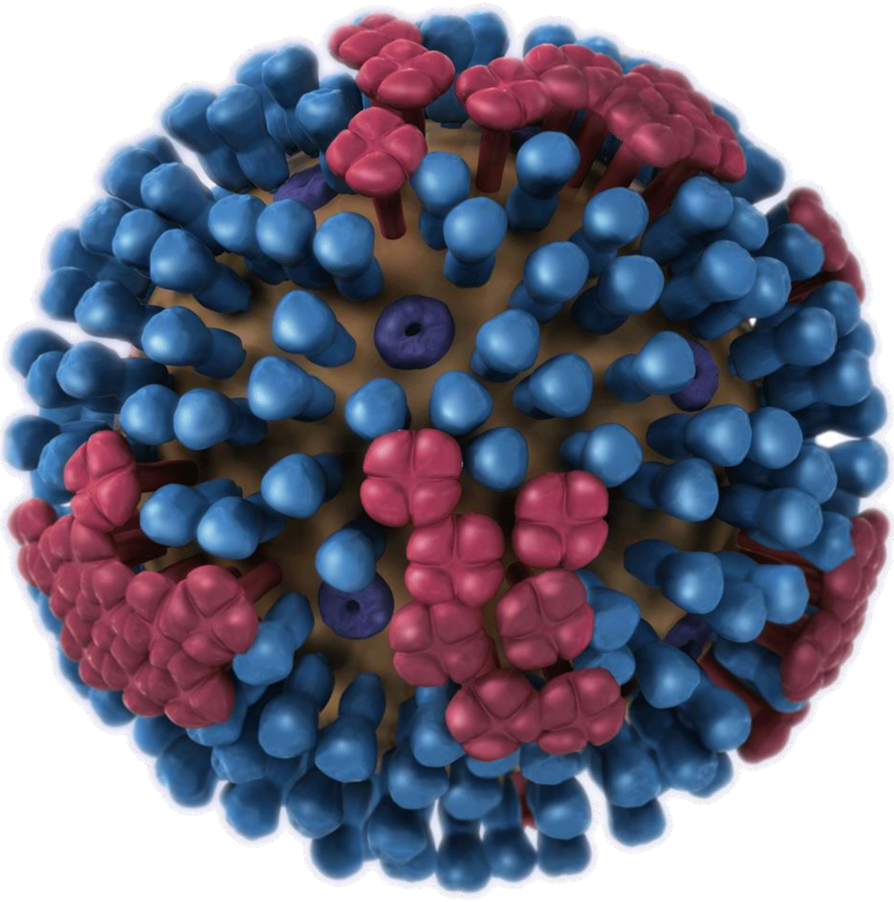


WRAIR- GEIS 'Operational Clinical Infectious Disease' Course

WRAIR
Walter Reed Army Institute of Research
Soldier Health • World Health

Influenza

I had a little bird,
And its name was Enza.
I opened the window
And in-flew-enza.*



*Children's skipping rhyme during the 1918 Spanish Influenza pandemic.

www.cdc.gov

Influenza Virus

- Family: Orthomyxoviridae
- First isolated 1933
- 8 single stranded, negative sense RNA molecules
- Encodes for 10 proteins
  – Nucleoprotein (NP), Matrix (M) protein
  – Important surface glycoproteins
    - Hemagglutinin (HA)
    - Neuraminidase (NA)

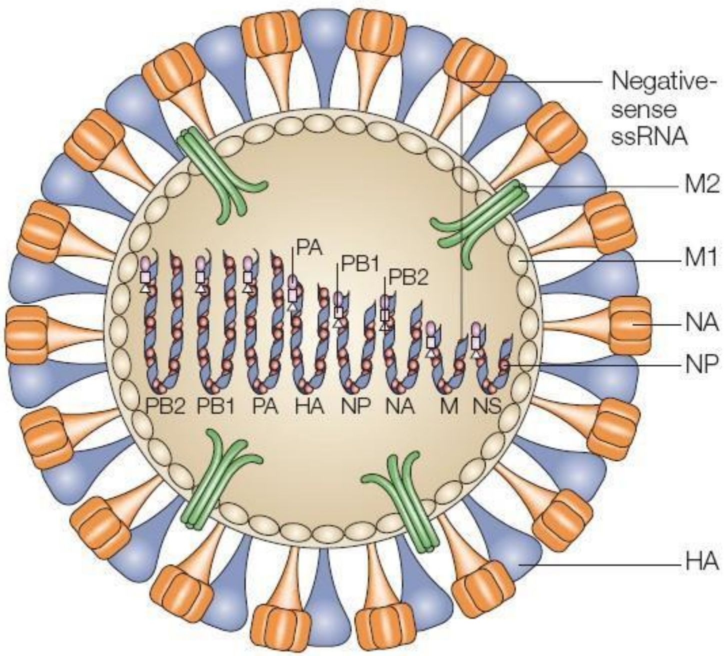


Figure 1 | **Schematic diagram of an influenza A virus virion.** Two surface glycoproteins, haemagglutinin (HA) and neuraminidase (NA), and the M2 ion-channel protein are embedded in the viral envelope, which is derived from the host plasma membrane. The ribonucleoprotein complex comprises a viral RNA segment associated with the nucleoprotein (NP) and three polymerase proteins (PA, PB1 and PB2). The matrix (M1) protein is associated with both ribonucleoprotein and the viral envelope. A small amount of non-structural protein 2 is also present, but its location within the virion is unknown.

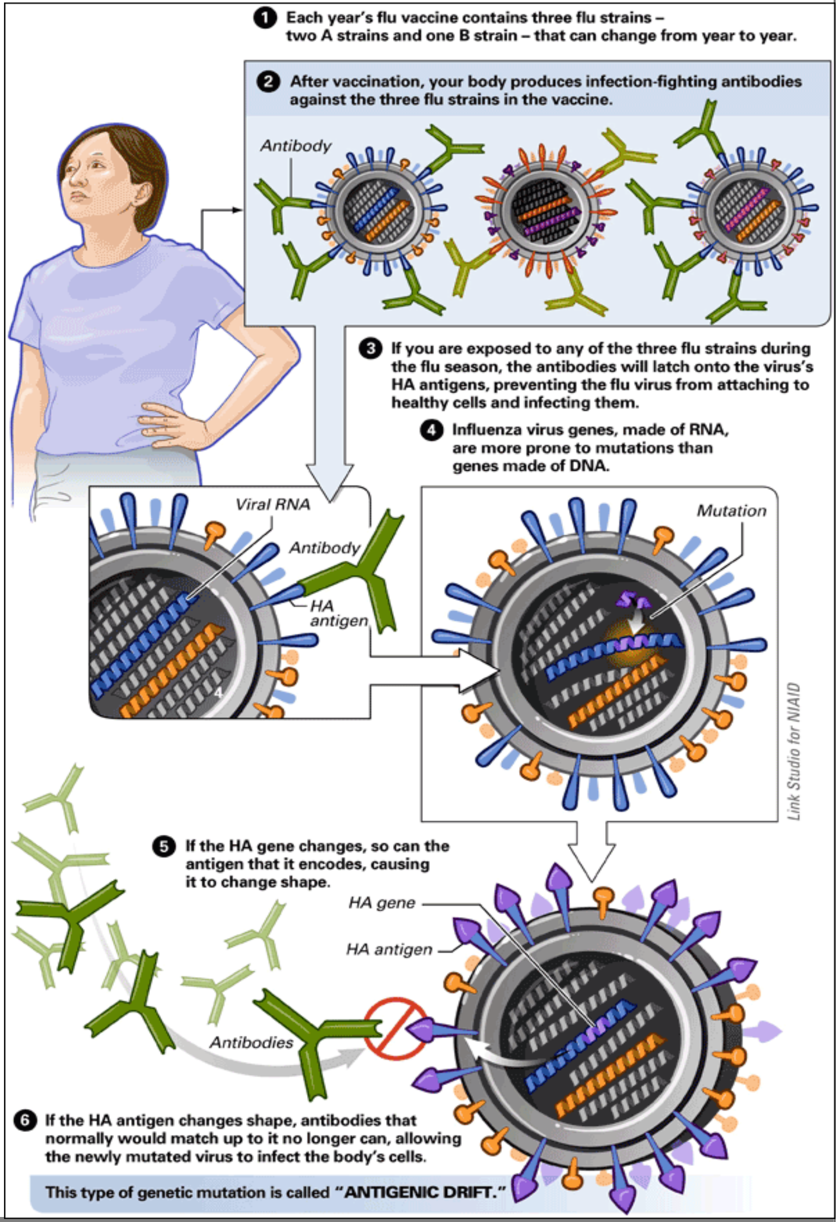
HA and NA

- Hemaglutinin initiates infection by binding to sialic acid residue on respiratory epithelial cells

- Neuraminidase liberates new virions after viral replication and help virions stay separated

Antigenic Drift

- Occurs in Influenza A and B
- Point mutations in the viral RNA genes
- Leads to production of new hemagglutinin or neuraminidase
- **<u>Annual occurrence</u>** to avoid host immune system
- Less severe ‘seasonal’ epidemics
- Occurs as virus spreads through a susceptible population



http://nieman.harvard.edu/Microsites/NiemanGuideToCoveringPandemicFlu/TheScience/HowFluVirusesChange.aspx

Case

- You are deployed to the Philippines. You see a 24 yo male pig farmer with no medical history, previously in excellent health. The patient appears very ill, complaining of fevers, diffuse myalgias, cough, and shortness of breath. The patient requires intubation, but dies a week later. You hear of several other locals with similar symptoms, some young adults with severe disease.

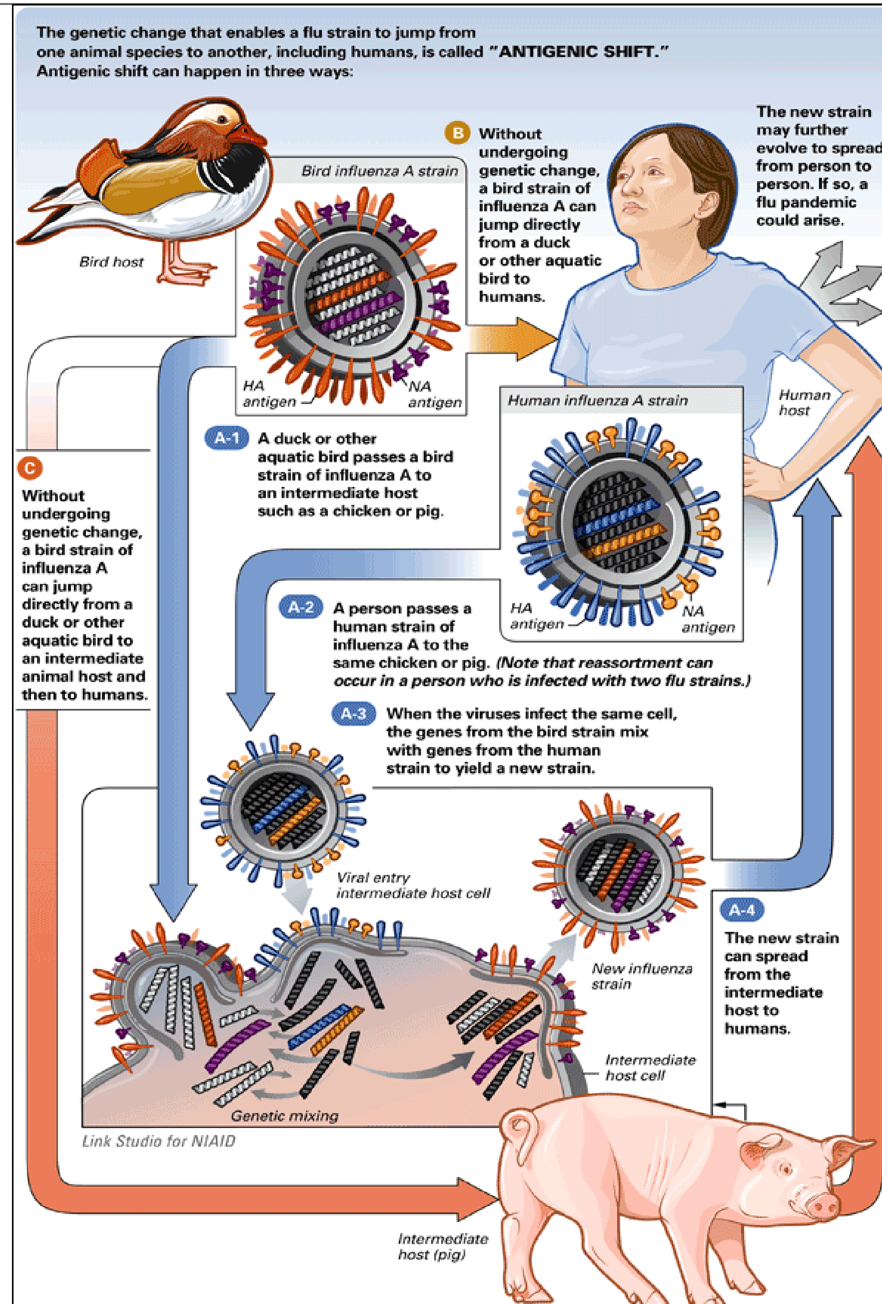
- Pulmonary aspirates sent on your patient return from the lab in AFRIMS (Bangkok). Samples sent on 3 different days were negative on 2 of the days, and positive for Influenza A on a single sample. Confirmatory testing has not been able to determine the viral subtype.

- WTF?! (i.e. What the Flu?)

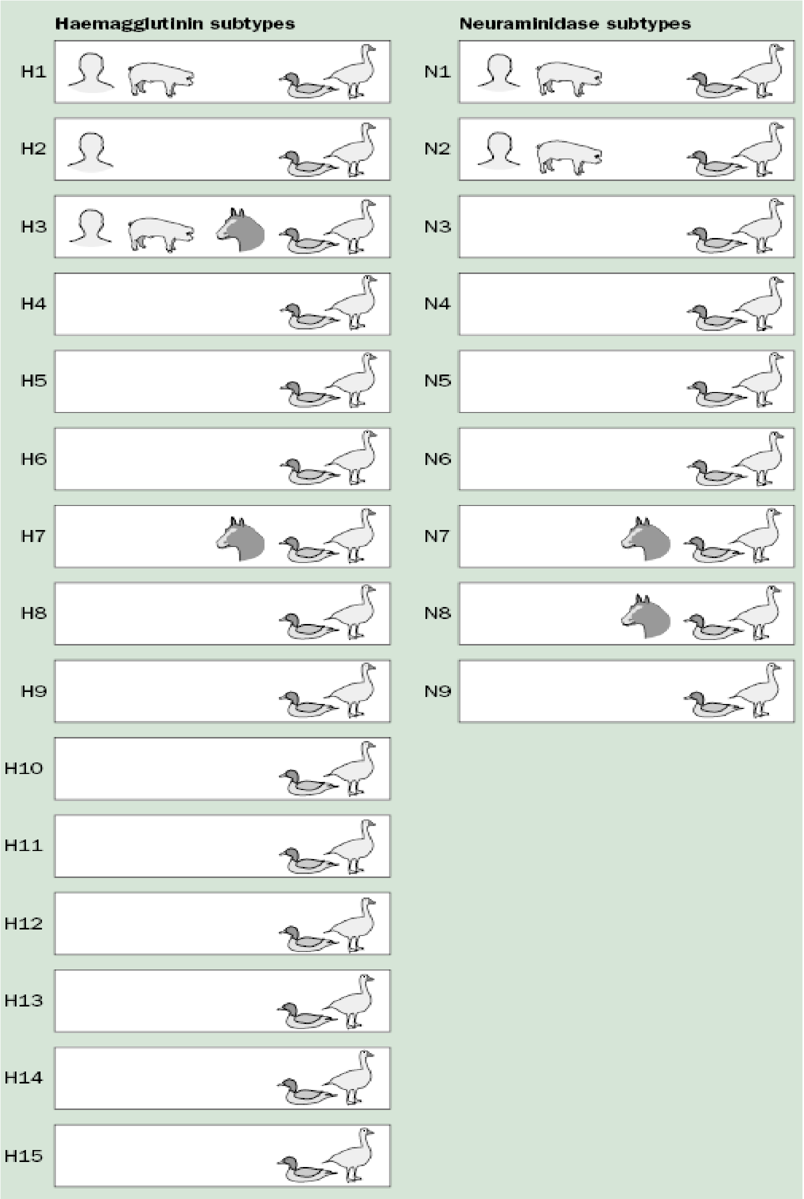
Antigenic Shift

- Major changes in HA and NA
- Influenza A viruses only
- Reassortment of viral genetic material between viruses co-infecting the same cell
- **<u>Pandemic strains</u>** result from exchange of genetic material between animal and human viruses
- No protective immunity in host
- Usually more rapidly spreading and severe infection

VIDEO OF INTEREST (1918 Spanish Flu):
http://www.youtube.com/watch?v=48Klc3DPdtk



- All HA and NA in birds
- Crossing of species is limited
  - Humans
    - H1, H2, H3
    - N1, N2
  - Horses
    - H7, N7
    - H3, N8
  - Pigs
    - H1, H3
    - N1, N2



Influenza Typing

- Classified based on antigenic differences in NP and M
- Influenza A viruses have various types of HA and NA
- Influenza B viruses **DO NOT** have shifts and major changes in HA and NA
- Example Nomenclature

  Type /Host / Place / Strain #/Year (Influenza subtype)

  A / Duck / Vietnam/ 11 / 04 (H5N1)

WRAIR

Influenza in the Tropics

- Less distinct ‘seasonal’ pattern vs. temperate regions
- **<u>Year round infections</u>**
- ‘Seasonal’ patterns vary by location
  - Peaks related to rainy seasons
  - Biannual peaks (rainy season and winter months)
  - Year round infection without clear peaks

Environmental Predictors of Seasonal Influenza Epidemics across Temperate and Tropical Climates

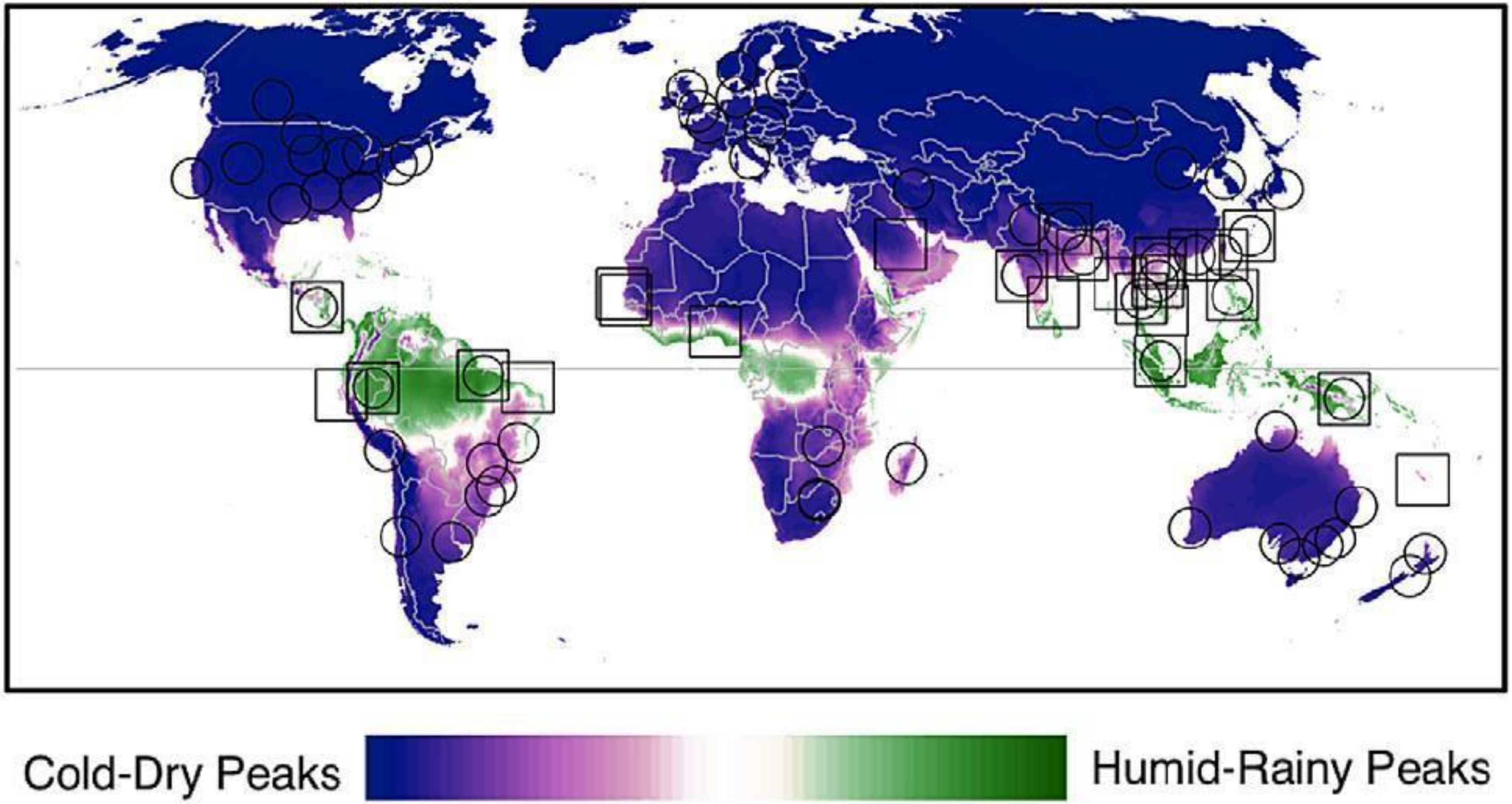
- Study conducted at 78 study sites globally
- Influenza infections peaked during low specific humidity and temperatures in areas where these values fell below threshold
- In areas with constant high humidity and temperature, influenza infections peaked in month of high precipitation

Citation: Tamerius JD, Shaman J, Alonso WJ, Bloom-Feshbach K, Uejio CK, et al. (2013) Environmental Predictors of Seasonal Influenza Epidemics across Temperate and Tropical Climates. PLoS Pathog 9(3): e1003194. doi:10.1371/journal.ppat.1003194

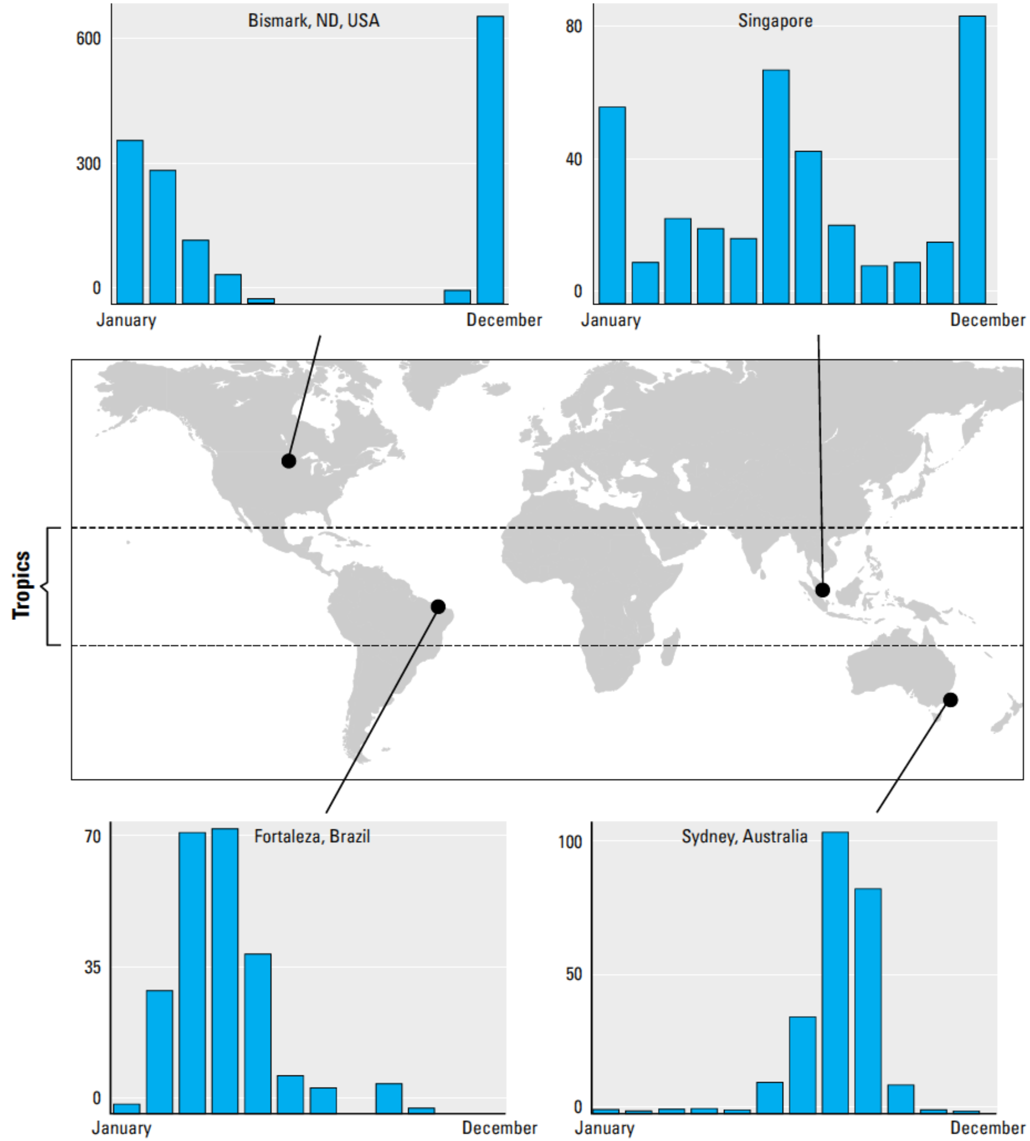
Editor: Steven Riley, Imperial College London, United Kingdom

Received August 28, 2012; **Accepted** December 26, 2012; **Published** March 7, 2013

Influenza in the tropics



Rainy Season = Influenza Peak



Tamerius et al. *Environ Health Perspect* 2011

Seasonal Influenza Vaccine

- 20 yo soldier is adamant that he does not want to get his flu vaccine because it “gave him the flu” last year the following day.

- Your response is….?

Seasonal Influenza Vaccine

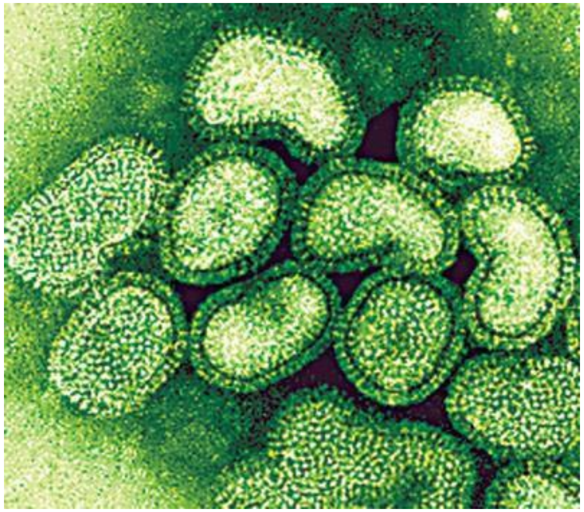
- You can't get the flu from the injection (it's inactivated virus)
- Flumist is a live attenuated virus, but other than causing runny nose and mild congestion for a few days it can't cause the flu in a healthy individual
- There are other viruses that cause the common cold that are circulating the same time of year
- It takes approximately 14 days to develop an immune response to the vaccine
- If there is a mismatch for that year (ahem…like this year), there is the possibility that you can develop influenza despite vaccination

Pandemic Influenza

- Influenza A virus introduction
  - Novel HA gene
  - No 'herd' immunity
  - Ability to spread efficiently among humans

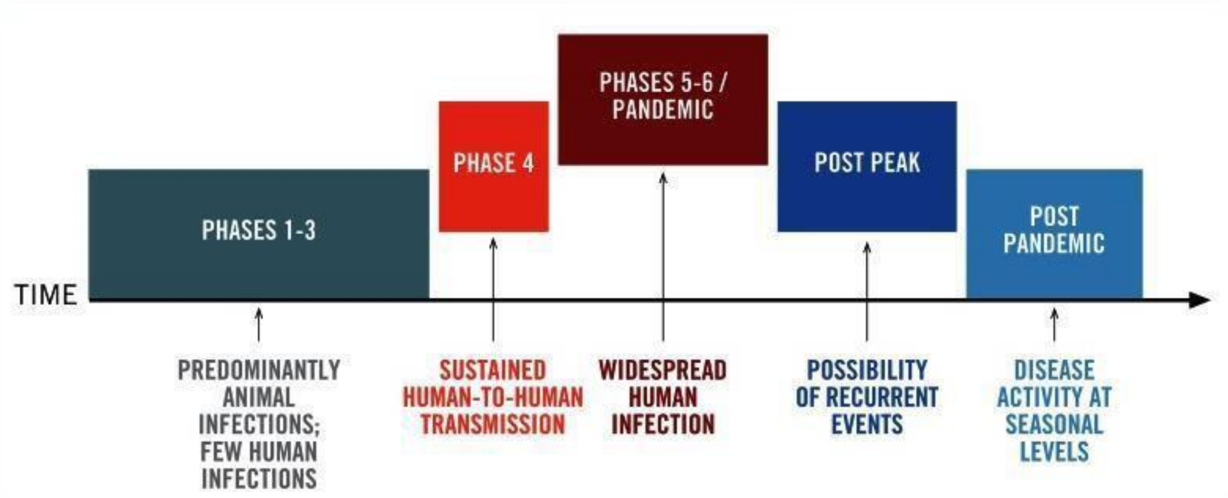
- Pandemics of 20th century
  - All originated from avian influenza viruses
  - Intervals of 11-39 years
  - **1918 (H1N1: Spanish)**
  - 1957 (H2N2: Asian)
  - 1968 (H3N2: Hong Kong)
  - 2009 (H1N1: US, Mexico)

- Pseudo- and Abortive pandemics
  - 1947 (H1N1: Japan/Korea/New Jersey)
  - 1976 (H1N1: New Jersey)
  - 1977 (H1N1: Soviet Union)



Pandemic Influenza Phases

- Phases 1-3: Mostly animal infections
- Phase 4: Human-human transmission
- Phase 5-6: Pandemic, widespread human infection
- Post Peak: possibility of recurrence
- Post Pandemic: Seasonal



Pandemic Influenza

- Severe influenza syndrome
  - Fever, cough, fatigue, shortness of breath
  - Abdominal pain, diarrhea, vomiting
  - No conjunctivitis

- Chest X-ray with bilateral infiltration, lobar collapse, focal consolidation
- Complications
  - Acute respiratory distress, renal failure, **bacterial superinfection**


1918 Influenza Pandemic

- 1/3 of the world's population infected
- Case fatality rates of >2.5%
- 3 waves: spring/summer, summer/fall, winter
- Unclear source of pandemic virus, limited capabilities

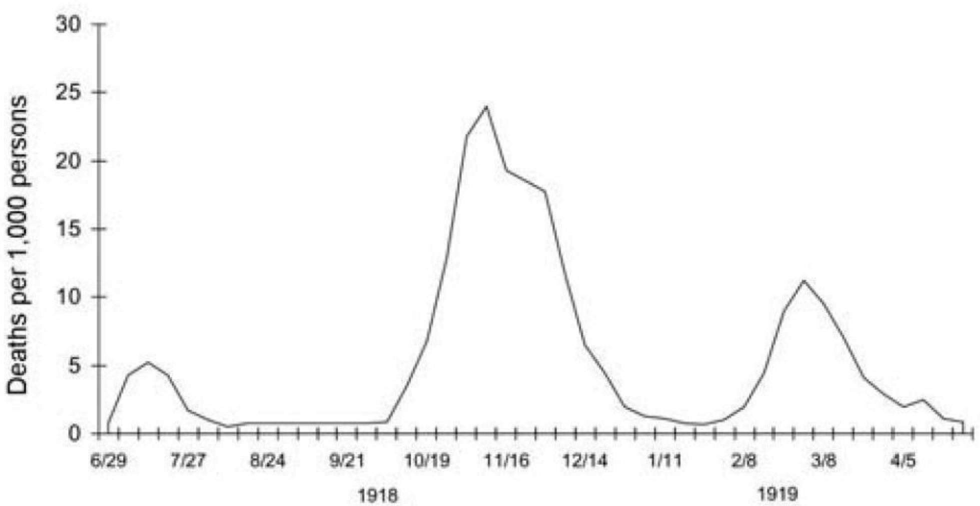


Figure 1. Three pandemic waves: weekly combined influenza and pneumonia mortality, United Kingdom, 1918–1919 (*21*).

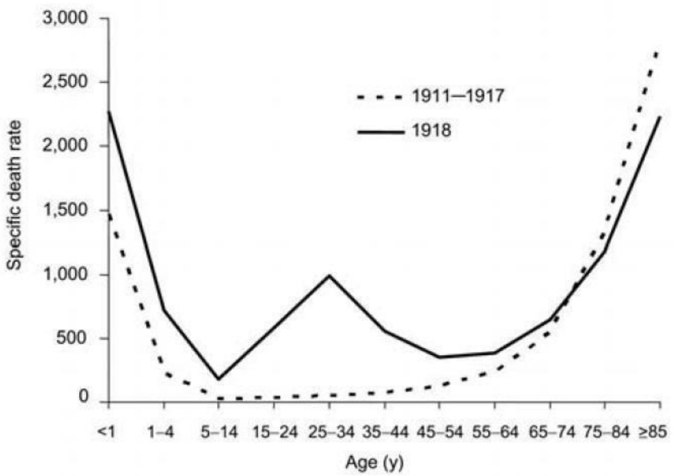


Figure 2. "U-" and "W-" shaped combined influenza and pneumonia mortality, by age at death, per 100,000 persons in each age group, United States, 1911–1918. Influenza- and pneumonia-specific death rates are plotted for the interpandemic years 1911–1917 (dashed line) and for the pandemic year 1918 (solid line) (*33,34*).

2009 H1N1 Pandemic

- ‘Swine flu’ first reported March 2009 in Mexico
- High human to human transmission, WHO pandemic level declared 6 June 2009
- Influenza A virus
  - Reassortment of 2 swine, one human strain, one avian strain

- Incubation: 1-4 days; viral shedding peak: 2-3 day into illness
- Secondary attack rate: 14-19%
- Viral shedding peaks first 2-3 days of illness

2009 H1N1 Pandemic

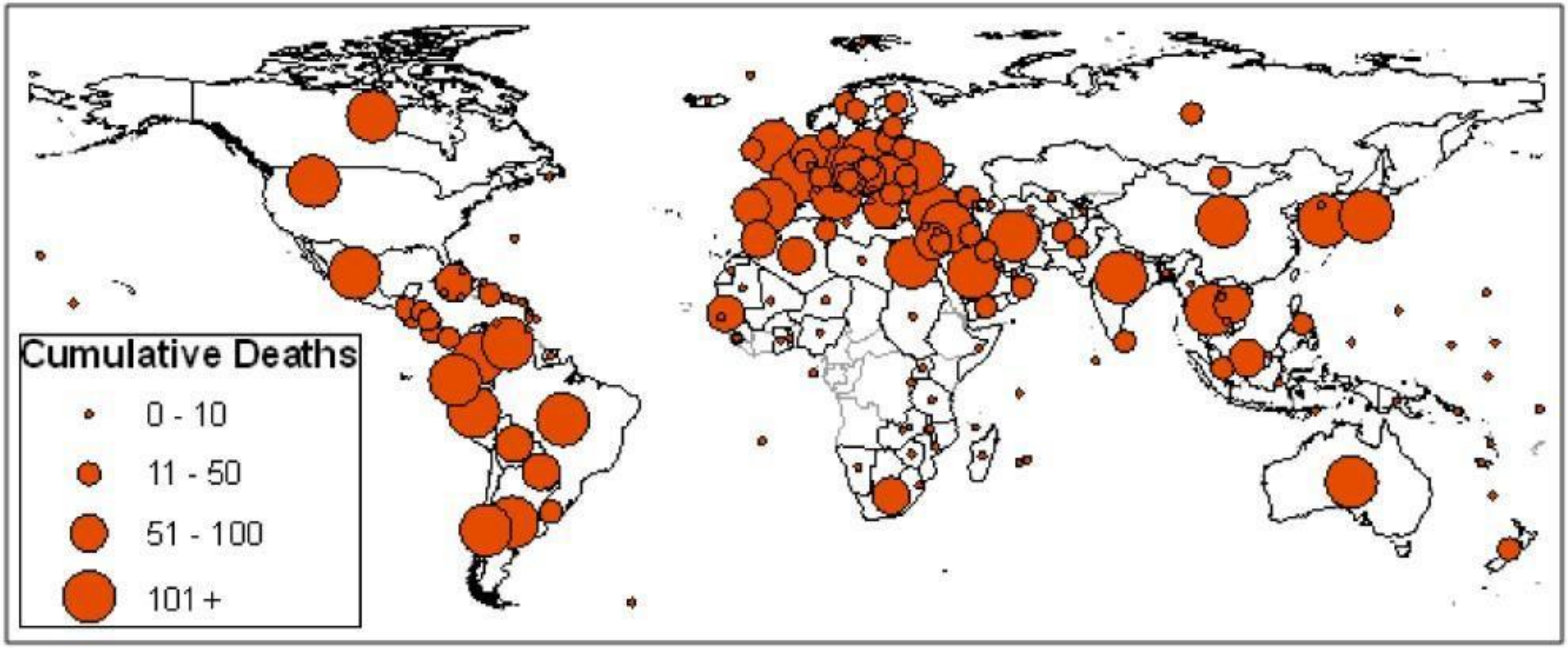


Figure 2: Map of cumulative global deaths from the 2009 H1N1 influenza pandemic, as of February 2010 (Data source: ECDC, 2010)

2009 H1N1 Pandemic

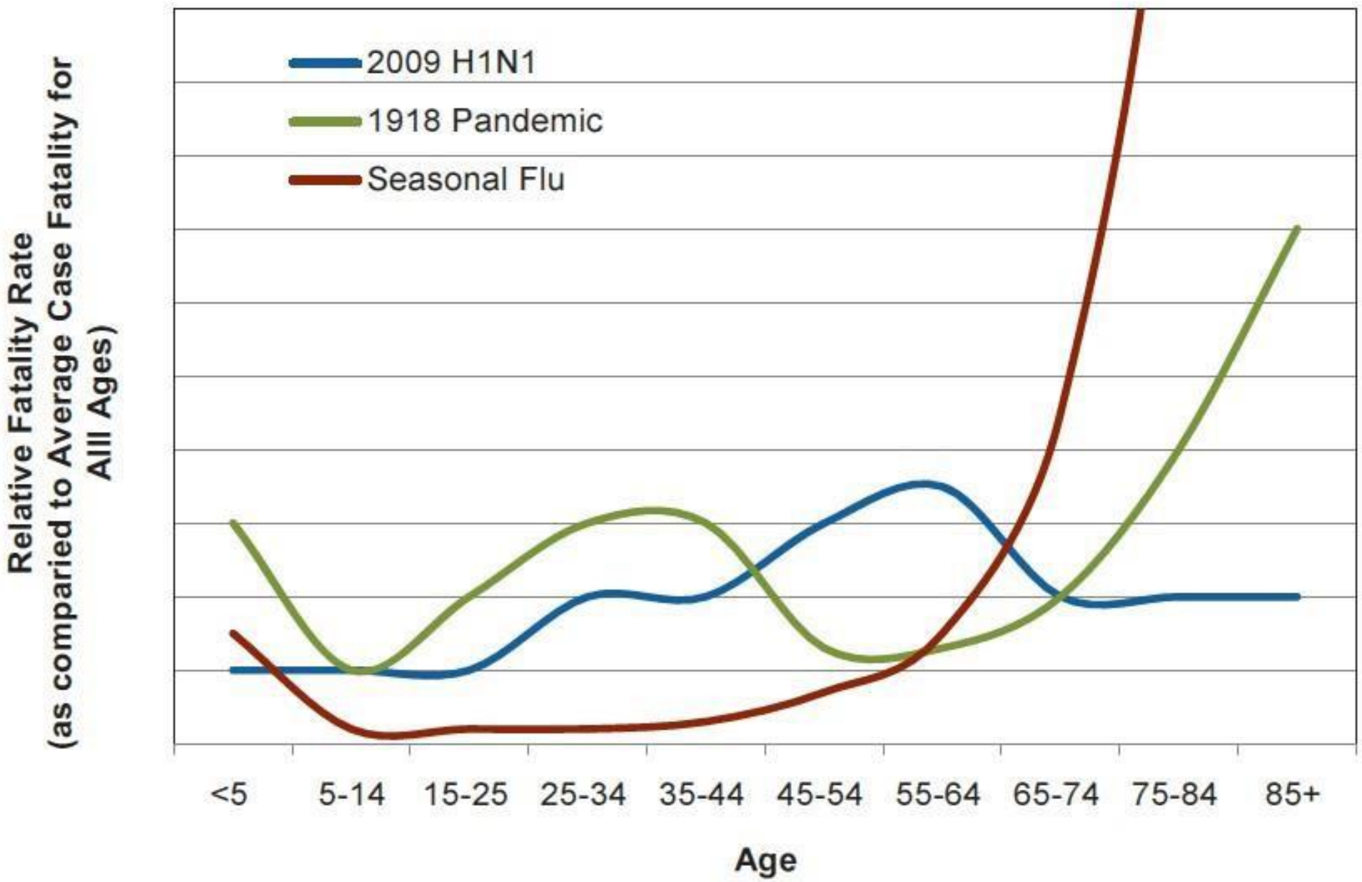


Figure 3: Age distribution of influenza mortality: comparing seasonal flu to the 1918 and 2009 pandemics

Lessons from 2009 pandemic

- Vigilance and surveillance for novel strains
- Identify at risk populations
- Limitations of laboratories and hospitals
- Educating the public about preventive measures
- Vaccine manufacturing and quality control
- Availability of antiviral drugs
- Each epidemic, pandemic is different (current treatments and technologies are on our side)

Avian Influenza

CDC

MMWR

Morbidity and Mortality Weekly Report

Outbreaks of Avian Influenza A (H5N2), (H5N8), and (H5N1) Among Birds — United States, December 2014–January 2015

Michael A. Jhung, MD, Deborah I. Nelson, PhD

Avian Influenza

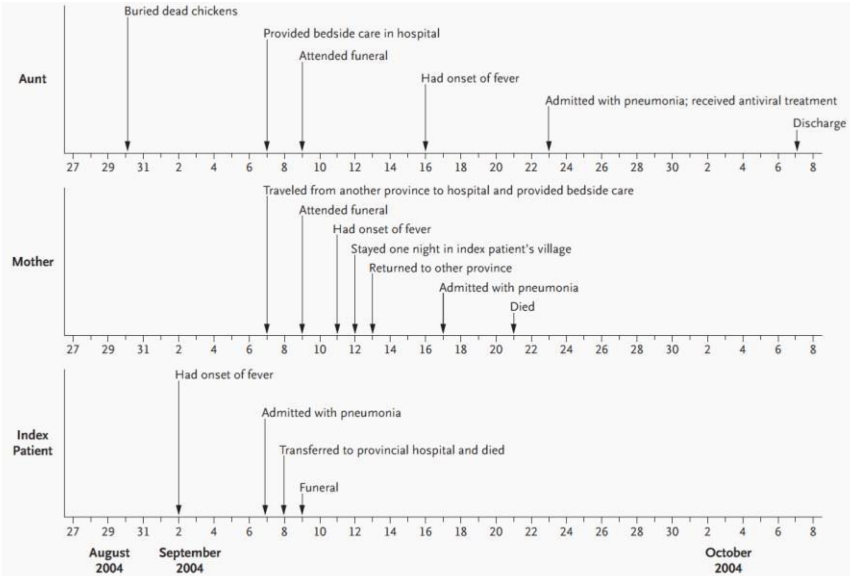
- Reservoir: Aquatic birds
- Transmission between birds
  - Direct
  - Indirect (fecal aerosols, water, feed, etc.)

- Clinically
  - Asymptomatic → Mild respiratory illness → Fatal systemic disease

- Most isolates are avirulent
- Epidemic fowl mortality caused by highly pathogenic varients
  - H5 and H7
  - Decreased egg production, respiratory disease, head edema, diarrhea, death

Probable Person-to-Person Transmission
of Avian Influenza A (H5N1)

N ENGL J MED 352;4 WWW.NEJM.ORG JANUARY 27, 2005



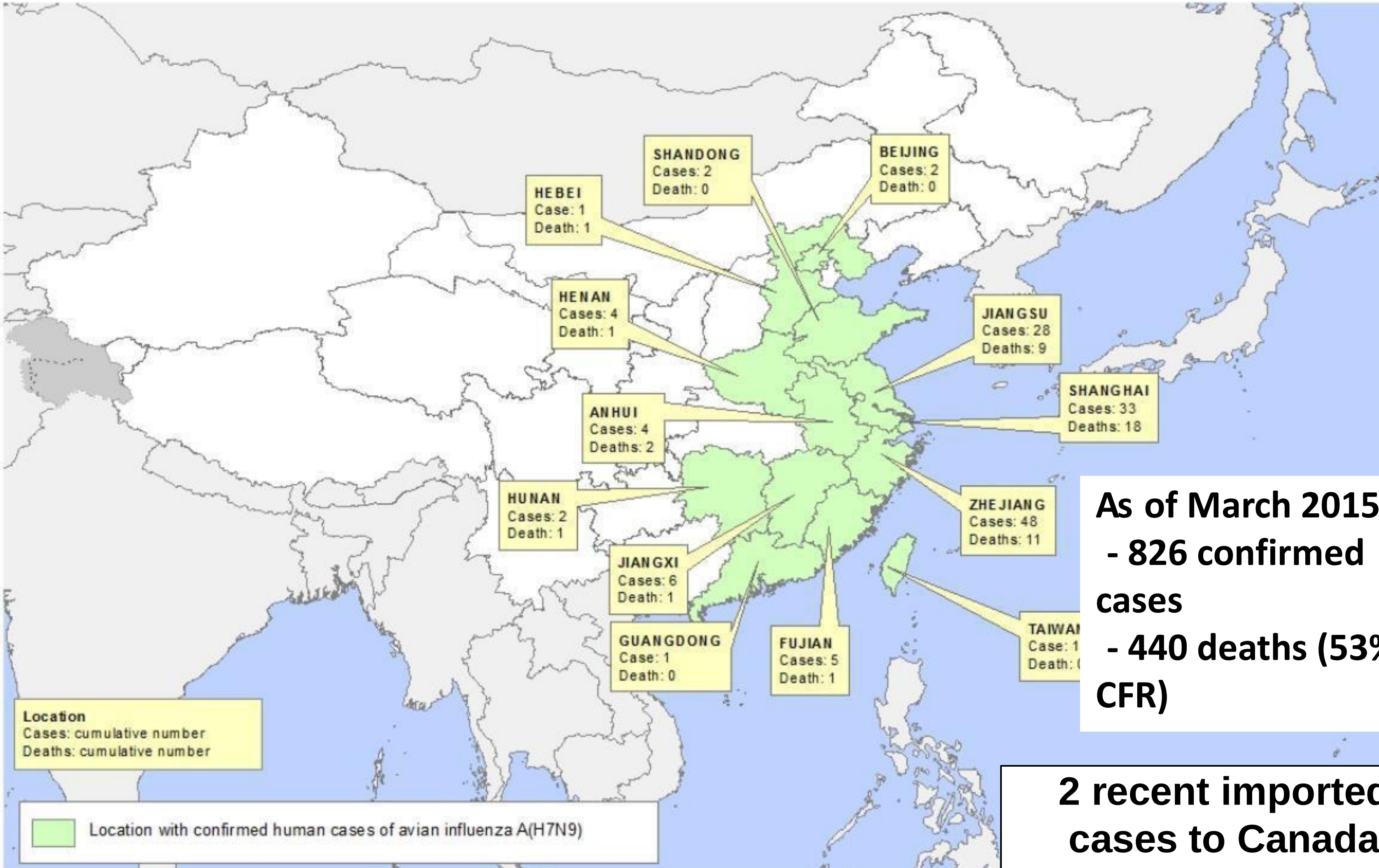
Probable person to person transmission of novel avian influenza A (H7N9) virus in Eastern China, 2013: epidemiological investigation

BMJ 2013;347:f4752 doi: 10.1136/bmj.f4752 (Published 6 August 2013)

Avian Influenza Human to Human Transmission

- A few reports of probable transmission among close family or hospital contacts
- WHO: limited non- sustained human to human spread

Avian Influenza A (H7N9)



As of March 2015
- 826 confirmed cases
- 440 deaths (53% CFR)

2 recent imported cases to Canada

Data as of 25 October 2013, 8:00 GMT+1
Source: WHO/GIP

Severe Illness from H5N1

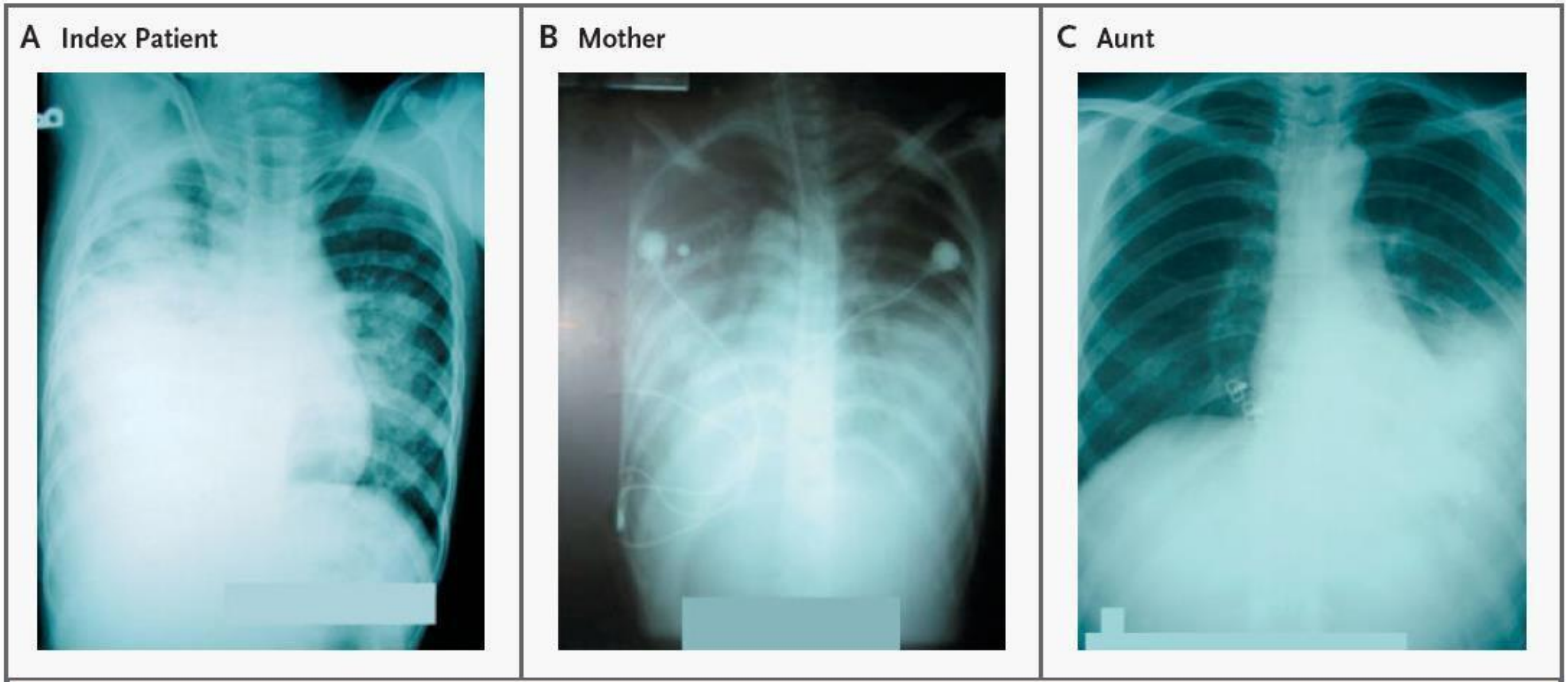


Figure 1. Chest Radiographs from the Three Patients with Avian Influenza A (H5N1).
Panel A shows a chest radiograph from the index patient, an 11-year-old girl, on day 6 of her illness. The image shows right-lower-lobe consolidation and patchy left-lower-lobe infiltrates. Panel B shows a radiograph from the girl's 26-year-old mother on day 9 of her illness. There is bilateral lower-lobe consolidation. Panel C shows a radiograph from the girl's 32-year-old aunt on day 7 of her illness; left-lower-lobe consolidation is visible.

N ENGL J MED 352;4 WWW.NEJM.ORG JANUARY 27, 2005

Severe Illness from H5N1

Outcome or Measure	Hong Kong, 1997 (N=18)	Thailand, 2004 (N=17)	Vietnam, 2004 (N=10)	Ho Chi Minh City, 2005 (N=10)	Cambodia, 2005 (N=4)
Hospital course — no. (%)					
Respiratory failure	8 (44)	13 (76)	9 (90)	7 (70)	4 (100)
Cardiac failure	NS	7 (41)	NS	0	NS
Renal dysfunction	4 (22)	5 (29)	1 (10)	2 (20)	NS
Antiviral therapy‖					
Amantadine	10 (56)	0	0	0	NS
Ribavirin	1 (6)	0	2 (20)	0	
Oseltamivir	0	10 (59)	5 (50)	10 (100)	
Corticosteroids**	5 (28)	8 (47)	7 (70)	5 (50)	NS
Inotropic agents	NS	8 (47)	2 (20)	NS	
Time from onset of illness to death — days					
Median	23	12	9	12.8†	8
Range	8–29	9–30	4–17	4–21	6–10
Deaths — no. (%)	6 (33)	12 (71)	8 (80)	8 (80)	4 (100)

N ENGL J MED 353;13 WWW.NEJM.ORG SEPTEMBER 29, 2005

Avoid These

Figure 2. The effect of highly pathogenic H5N1 virus on ducklings in Vietnam (photo T Tumpey).

Table 4. Exposures That May Put a Person at Risk for Infection with Influenza A (H5N1).*

Countries and territories where influenza A (H5) viruses have been identified as a cause of illness in human or animal populations since October 1, 2003

During the 7 to 14 days before the onset of symptoms, one or more of the following:

- Contact (within 1 m) with live or dead domestic fowl or wild birds or domestic ducks
- Exposure to settings in which domestic fowl were confined or had been confined in the previous 6 weeks
- Unprotected contact (within touching or speaking distance) with a person for whom the diagnosis of influenza A (H5N1) is confirmed or being considered
- Unprotected contact (within touching or speaking distance, 1 m) with a person with an unexplained acute respiratory illness that later resulted in severe pneumonia or death
- Occupational exposure†

Countries and territories where influenza A (H5) viruses have not been identified as a cause of illness in human or animal populations since October 1, 2003

During the 7 to 14 days before the onset of symptoms, close contact with an ill traveler from one of the areas with known influenza A (H5) activity, history of travel to a country or territory with reported avian influenza activity due to influenza A (H5N1) in the animal populations, or living in an area in which there are rumors of the death of domestic fowl, and one or more of the following:

- Contact (within 1 m) with live or dead domestic fowl or wild birds in any setting or with domestic ducks
- Exposure to settings in which domestic fowl were confined or had been confined in the previous 6 weeks
- Contact (within touching or speaking distance) with a patient with a confirmed case of influenza A (H5)
- Contact (within touching or speaking distance) with a person with an unexplained acute respiratory illness that later resulted in severe pneumonia or death
- Occupational exposure†

* These summaries do not present formal WHO guidelines, although they contain content from WHO documents.[1]

† At-risk occupations include domestic-fowl worker, worker in a domestic-fowl processing plant, domestic-fowl culler (catching, bagging, or transporting birds or disposing of dead birds), worker in a live-animal market, chef working with live or recently killed domestic fowl, dealer or trader in pet birds, health care worker, and a worker in a laboratory processing samples possibly containing influenza A (H5N1) virus.

N ENGL J MED 353;13 WWW.NEJM.ORG SEPTEMBER 29, 2005

Pandemic & Avian Influenza: Management

- Early suspicion and recognition
- Isolation and testing
- Symptom management
- Neuraminidase inhibitors
  - Oseltamivir (oral), zanamivir (inhaled), and peramivir (IV)
  - Effective for both influenza A and B (unlike amantadine)
  - Give within 48 hr of symptom onset
  - Prevention of H5N1 but resistance develops rapidly
- Vaccine if available
  - Pandemic H1N1 influenza vaccine in 2009-2010
  - H5N1 avian influenza vaccine manufactured by Sanofi Pasteur approved by FDA in 2007
  - Testing H7N9 avian influenza vaccine (NIH sponsored)

Good Rule of Thumb:
Severe Respiratory Disease → *isolate patient* until you know you're dealing with

Oseltamivir Treatment

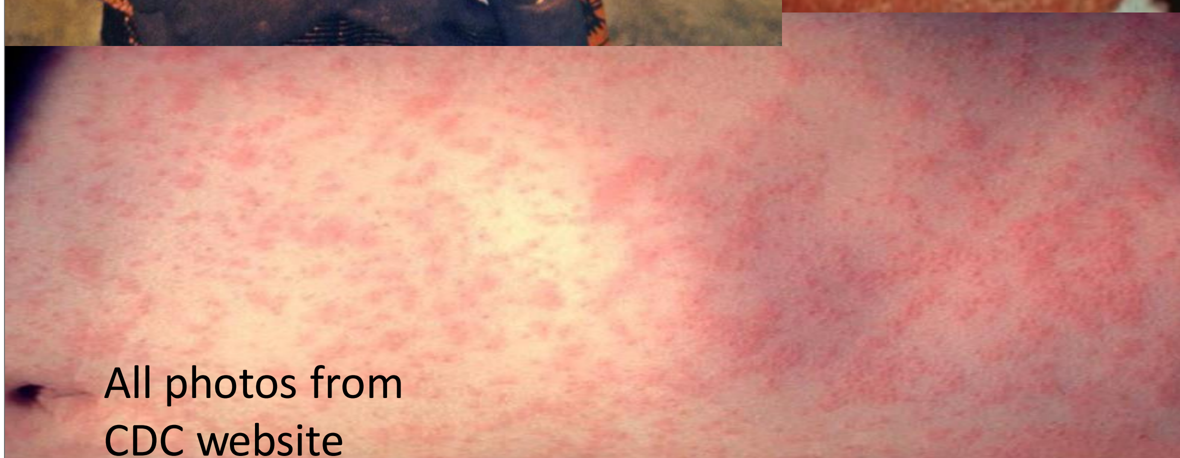
- Shortens symptoms and may reduce risk of complications, especially **<u>started within 48 hrs</u>**.
- Highest benefit:
  - Hospitalized, children < 2, adults > 65, chronic illness, immunocompromised, pregnant, those < 19 and receiving aspirin therapy, American Indians/Alaska Natives, morbidly obese, nursing home residents
- Do not wait for laboratory confirmation
- **Standard dose is 75 mg twice daily for 5 days**
  - Dose adjust but approved for 2 weeks and older
- Side effects: mostly nausea, vomiting, neuropsychiatric in Japan.

Oseltamivir Prophylaxis

- CDC dose NOT recommend widespread prophylaxis use.
- Vaccination and close monitoring as alternative
- 70-90% effective
- **75 mg once daily, exposure time + 7 days**
  - Likely not helpful to start > 48 hrs since exposure.
  - 2 weeks after last case in long-term care facilities

Other Common Respiratory Viruses

- Adenovirus
  - 51 serotypes, types 1-7 responsible for most infections.
  - Oral adenovirus type 4 & 7 vaccine for military recruits
- Respiratory syncytial virus (RSV)
  - Annual epidemics, bronchiolitis in infants
- Coronaviruses
  - Common Cold virus
  - Severe respiratory infections: SARS CoV (2003), MERS CoV (2013)
- Human metapneumovirus (HMPV) = Similar to RSV
- Parainfluenza virus = Four types, type 3 in spring and early summer
- Rhinoviruses
  - Common cold virus, 100 + serotypes, year-round in tropics



All photos from
CDC website

Measles

- Incubation period typically 7-14 days
- **Highly contagious** (**AIRBORNE** transmission)---- **154 cases** in 2015
  - Can spread to others up to 4 days prior to rash
  - Adults can be affected

- Typical presentation (high fever, cough, runny nose, conjunctivitis, and rash erupting a few days later)
  - Rash spreads from face and head downward (fever spikes)

- Complications (This kills kids: 1 to 2 kids/1000 die)
  - ~25% require hospitalization
  - Ear infections in 10% (can result in hearing loss)
  - Diarrhea (10%)
  - Pneumonia (5%) – **most common cause of death**
  - Encephalitis (0.1%) – can result in major neurologic sequelae
  - Subacute Sclerosing Panencephalitis (SSPE)
    - Rare, but fatal occurring ~10 years after full recovery from infection

Measles Cases and Outbreaks

January 1 to December 11, 2015*

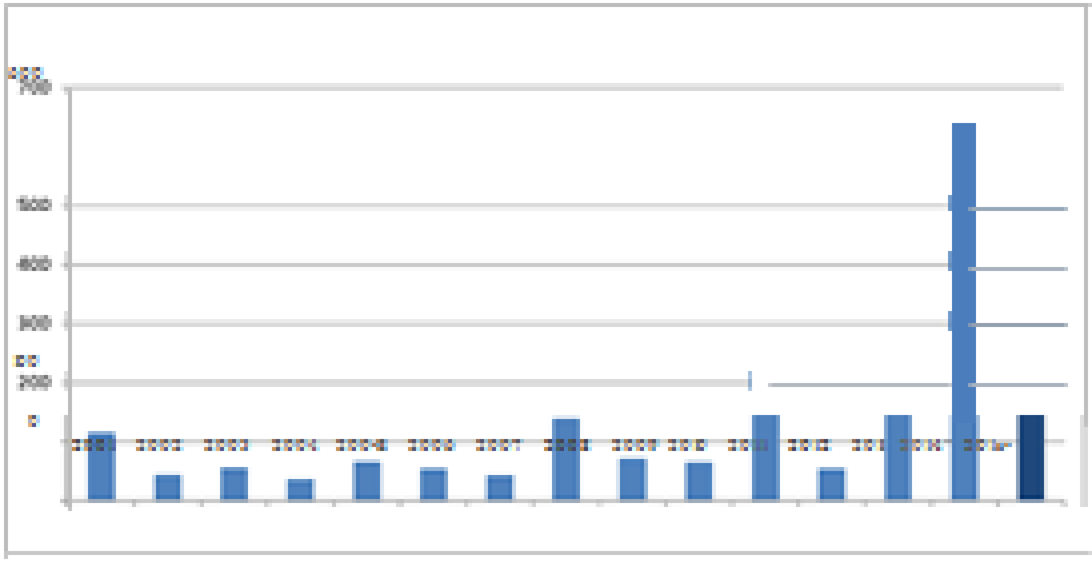
189 Cases

reported in 24 states and the District of Columbia: Alaska, Arizona, California, Colorado, Delaware, Florida, Georgia, Illinois, Massachusetts, Michigan, Minnesota, Missouri, Nebraska, New Jersey, New York, Nevada, Ohio, Oklahoma, Pennsylvania, South Dakota, Texas, Utah, Virginia, Washington

5 Outbreaks

representing 80% of reported cases this year

U.S. Measles Cases by Year



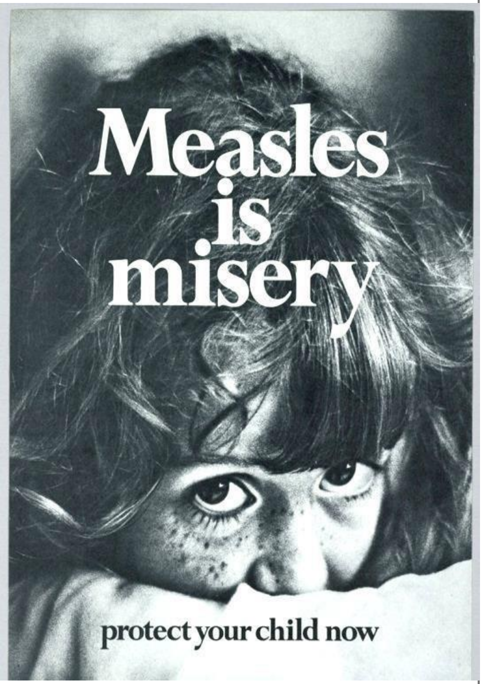
*Provisional data reported to CDC's National Center for Immunization and Respiratory Diseases

Koplik Spots

CDC

Measles

- Vaccination with MMR
  - Single dose is 93% protective (97% with 2 doses)
    - First dose just after first birthday (can get it as early as 6 mo*)
    - Second dose generally ages 4 to 6 years**
  - Not available in many developed nations
    - 20 million cases worldwide with 146,000 deaths
- Treatment
  - Supportive care
  - Monitor for bacterial superinfections
  - Vitamin A once daily x 2 days (50k to 200k IU/dose)
  - Ribavirin?

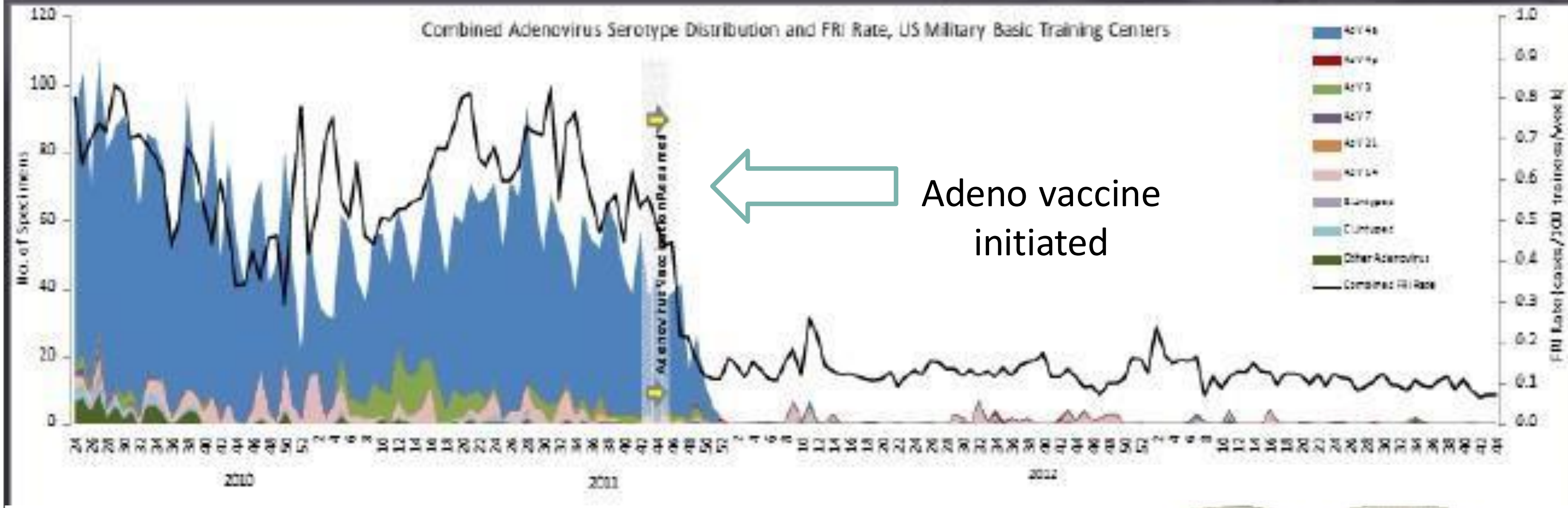


all-that-is-interesting.com

*If traveling overseas, but would need 2 additional doses after first birthday

**Can get second dose as early as 28 days after first dose

Impact of Adenovirus type 4 & 7 Vaccination Among Recruits at Eight Training Centers



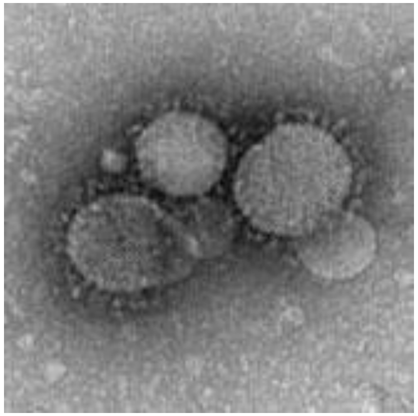
Case

- You are deployed to Kuwait and you admit a young male SM, smoker with flulike illness, with fevers, shortness of breath and intermittent diarrhea. The SM develops ARDS and is intubated in critical condition. Within 4 days of admission, 2 of your staff are developing similar symptoms.

- What might this be?

Coronavirus

- Meaning 'crown or halo'
- Large, positive sense RNA virus
- Family *Coronaviridae*
- Infects humans, mammals, birds
- **Severe acute respiratory syndrome coronavirus**
  - (SARS-CoV)
  - Rapid human to human spread worldwide
  - 774 probable deaths, 10% fatality rate
  - Started in Hong Kong Feb. 2003
    - Civet cats and other small mammals to humans?
  - Delayed peak transmission period
    - Rare within first 5 days of symptom onset
    - Easier recognition, isolation, and interruption
  - **<u>No cases since 2004</u>**



CDC Image

Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

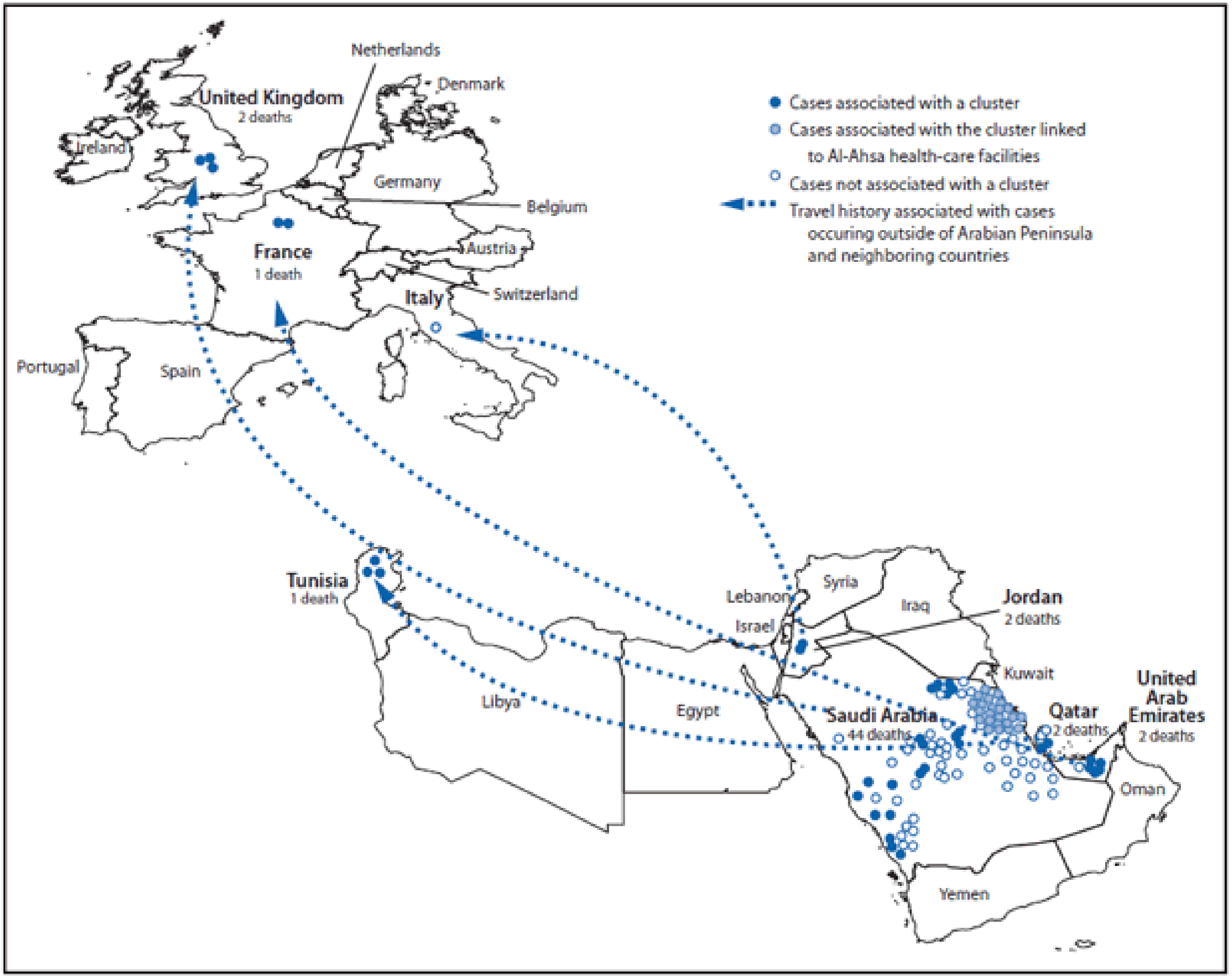
- Severe, contagious, respiratory illness
  - 376 deaths in 1026 lab confirmed cases (37% case fatality rate) as of 23 FEB 2015
- First cluster in Jordan, April 2012
- First Saudi Arabia case, June 2012
- Cluster among family contacts, returning travelers in Europe
- Nosocomial transmission (24% of cases)
- Reservoir (bats ? **camels** ⍰ EID 2014 Dec; 20: 1999)
- Geographically diverse animal reservoir, initial emergence in July 2011, sporadic introduction into humans and human-to- human transmission

MERS-CoV

- **Countries in or near the Arabian Peninsula with Cases**
- Saudi Arabia
- United Arab Emirates (UAE)
- Qatar
- Oman
- Jordan
- Kuwait
- Yemen
- Lebanon
- Iran

- **Countries with Travel-associated Cases**
- United Kingdom (UK)
- France
- Tunisia
- Italy
- Malaysia
- Philippines
- Greece
- Egypt
- United States of America (USA)
- Netherlands
- Algeria
- Austria
- Turkey

CDC, updated Jul 31, 2014



CDC MMWR Sept 27, 2013, 62(38); 793-6

Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study

Lancet Infect Dis 2013; 13: 752–61

Abdullah Assiri*, Jaffar A Al-Tawfiq*, Abdullah A Al-Rabeeah, Fahad A Al-Rabiah, Sami Al-Hajjar, Ali Al-Barrak, Hesham Flemban, Wafa N Al-Nassir, Hanan H Balkhy, Rafat F Al-Hakeem, Hatem Q Makhdoom, Alimuddin I Zumla*, Ziad A Memish*

	Patients (n=47)
Fever	46 (98%)
Fever with chills or rigors	41 (87%)
Cough	39 (83%)
Dry	22 (47%)
Productive (sputum)	17 (36%)
Haemoptysis	8 (17%)
Shortness of breath	34 (72%)
Chest pain	7 (15%)
Sore throat	10 (21%)
Runny nose	2 (4%)
Abdominal pain	8 (17%)
Nausea	10 (21%)
Vomiting	10 (21%)
Diarrhoea	12 (26%)
Myalgia	15 (32%)
Headache	6 (13%)

Table 3: **Symptoms of Middle East respiratory syndrome in 47 Saudi cases at presentation**

	Patients (n=47)	Deaths (%)*
Any comorbidity	45 (96%)	28 (60%)
Diabetes	32 (68%)	21 (66%)
Chronic kidney disease	23 (49%)	17 (74%)
Chronic heart disease	13 (28%)	10 (77%)
Hypertension	16 (34%)	13 (81%)
Chronic lung disease	12 (26%)	10 (83%)
Obesity	8 (17%)	5 (63%)
Smoking	11 (23%)	7 (64%)
Malignant disease	1 (2%)	1 (100%)
Steroid use	3 (6%)	3 (100%)

*Proportion of patients who died according to comorbidity.

Table 4: **Comorbidities in 47 Saudi cases of Middle East respiratory syndrome**

Overall CFR = 36%

Any comorbidity = 60%

MERS Co-V

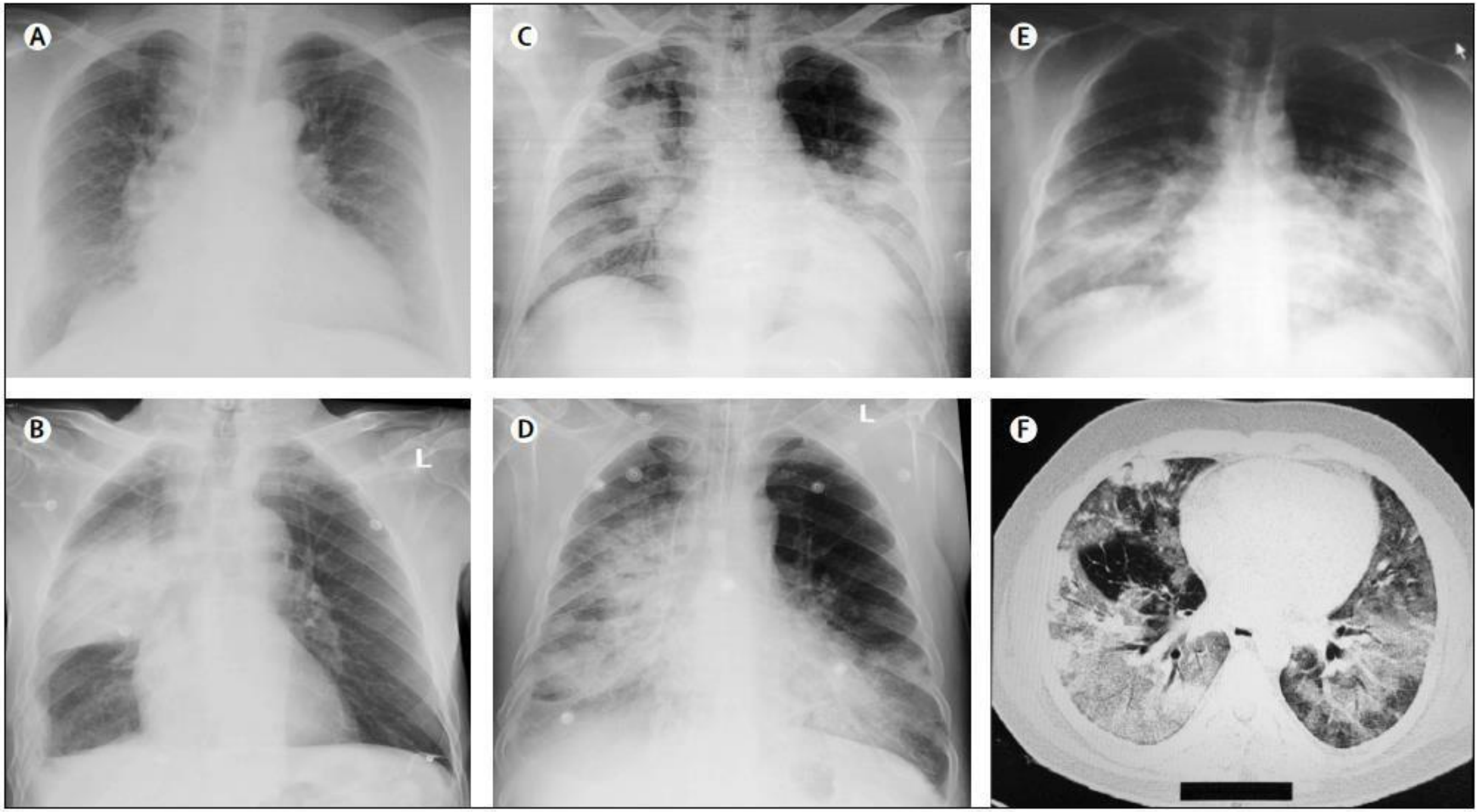


Figure 1: **Imaging findings at presentation in Saudi patients with Middle East respiratory syndrome**
(A) Chest radiograph of a 61-year-old man, showing bilateral fine reticulonodular air-space opacities, increased vascular markings, and cardiomegaly. (B) Chest radiograph of an 83-year-old man, showing right lung consolidation, right basal pleural thickening, and reticulonodular air-space opacities; rib fractures on the right are old. (C) Chest radiograph of a 56-year-old man, showing extensive bilateral extensive diffuse and focal alveolar space opacities, with opacification of the left lower lobe. (D) Chest radiograph of a 67-year-old man, showing extensive bilateral disease, with diffuse alveolar space densities, opacification, reticulonodular opacities, and bronchial wall thickening. (E) Chest radiograph of a 49-year-old man, showing extensive bilateral mid and lower zone disease, with diffuse reticulonodular alveolar space opacities. A thoracic CT scan in the same patient (F) shows extensive bilateral opacities and ground-glass reticulonodular shadowing and bronchiolar wall thickening.

Lancet Infect Dis 2013; 13: 752-61

Korea MERS cases at 180; studies note outbreak patterns

Filed Under: MERS-CoV

Lisa Schnirring | Staff Writer | CIDRAP News | Jun 25, 2015

Share Tweet LinkedIn Email Print & PDF

- 89% cases traced to 3 hospital-linked 'super-spreading' events
- Pattern resembles Middle East cases
  - Spread is slow beyond hospital-linked cases
- Incubation times longer in tertiary infected compared to those secondarily infected
- Better patient contact tracing could have prevented spread

MERS Co-V vs. SARS

	MERS-CoV	SARS, global[27 34]
Demographic factors		
Date of first case report (place)	April, 2012 (Jordan); June, 2012 (first Saudi case)	November, 2002 (China)
Mean (95% CI) incubation period (days)	5·2 (1·9–14·7); range 2–13	4·6 (3·8–5·8); range 2–14
Serial interval (days)	7·6	8·4
Age distribution	98% adults, 2% children	93% adults, 5–7% children
Mean (range) age (years)	56 (14–94)	39·9 (1–91)
Sex distribution	77% male, 23% female	43% male, 57% female
Sex ratio (male:female)	3·3:1	1:1·3
Clinical features		
Mortality	55%	0–40%
Case-fatality rate (overall)	Undefined	9·6%
In patients with comorbidities	60%	1–2%
Mean time from onset to death (days)	16·5	23·7

Lancet Infect Dis 2013; 13: 752–61

Current Guidance – MERS-CoV

- All cases linked to travel or residence in affected areas
- Assess risk, suspect disease
- Lower respiratory tract specimen for rRT-PCR preferred
  - Nasopharygeal wash or swabs
  - Serum for PCR and serologic testing
  - Stool for PCR
- Follow up serology testing
- Isolation Precautions
  - Airborne for suspected cases
    - For SARS, CDC: 'airborne precaution preferred'
  - Other standard AND contact precautions


N95 Mask

Image from Bing search engine "N95 mask"

Current Guidance – MERS-CoV: Case Definition

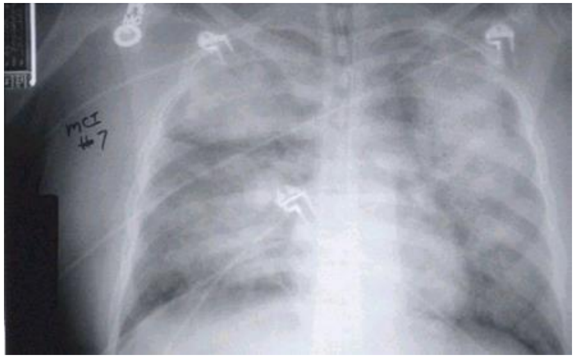
- **PATIENT UNDER INVESTIGATION (PUI) PER CDC WEBSITE:**
  - FEVER AND PNEUMONIA OR ARDS **AND**:
    - A HISTORY OF TRAVEL FROM COUNTRIES IN OR NEAR THE ARABIAN PENINSULA WITHIN 14 DAYS BEFORE SYMPTOM ONSET, **OR**
    - CLOSE CONTACT WITH A SYMPTOMATIC TRAVELER WHO DEVELOPED FEVER AND ACUTE RESPIRATORY ILLNESS (NOT NECESSARILY PNEUMONIA) WITHIN 14 DAYS AFTER TRAVELING FROM COUNTRIES IN OR NEAR THE ARABIAN PENINSULA[1] **OR**
    - A MEMBER OF A CLUSTER OF PATIENTS WITH SEVERE ACUTE RESPIRATORY ILLNESS (E.G., FEVER AND PNEUMONIA REQUIRING HOSPITALIZATION) OF UNKNOWN ETIOLOGY IN WHICH MERS-COV IS BEING EVALUATED, IN CONSULTATION WITH STATE AND LOCAL HEALTH DEPARTMENTS.

OR

  - FEVER AND SYMPTOMS OF RESPIRATORY ILLNESS AND BEING IN A HEALTHCARE FACILITY WITHIN 14 DAYS BEFORE SYMPTOM ONSET IN A COUNTRY OR TERRITORY IN OR NEAR THE ARABIAN PENINSULA IN WHICH RECENT HEALTHCARE-ASSOCIATED CASES OF MERS HAVE BEEN IDENTIFIED.

Hantavirus Pulmonary Syndrome

- Bunyavirus, enveloped, neg. SS RNA
- New World Hantavirus
    - ~300 cases per year, mortality up to 50%
    - Sporadic cases in the Americas: US, Canada, Argentina, Bolivia, Brazil, Chile, Panama, Paraguay, Uruguay
- Mice and rats are reservoirs
    - Urine, dropping, nesting materials are aerosolized and inhaled by humans
    - Bites and ingestion of contaminated food
    - Barns, outbuildings, and shed are exposure sites
- Incubation 1-4 weeks, initially non-specific myalgia, HA, chills, nausea, vomiting, GI symptoms
- Shortness of breath and cough develops later
    - Rapidly progressive cardiopulmonary phase
    - Bilateral infiltrates, pulmonary edema
- Conjunctival injection, renal involvement, and hemorrhage reported

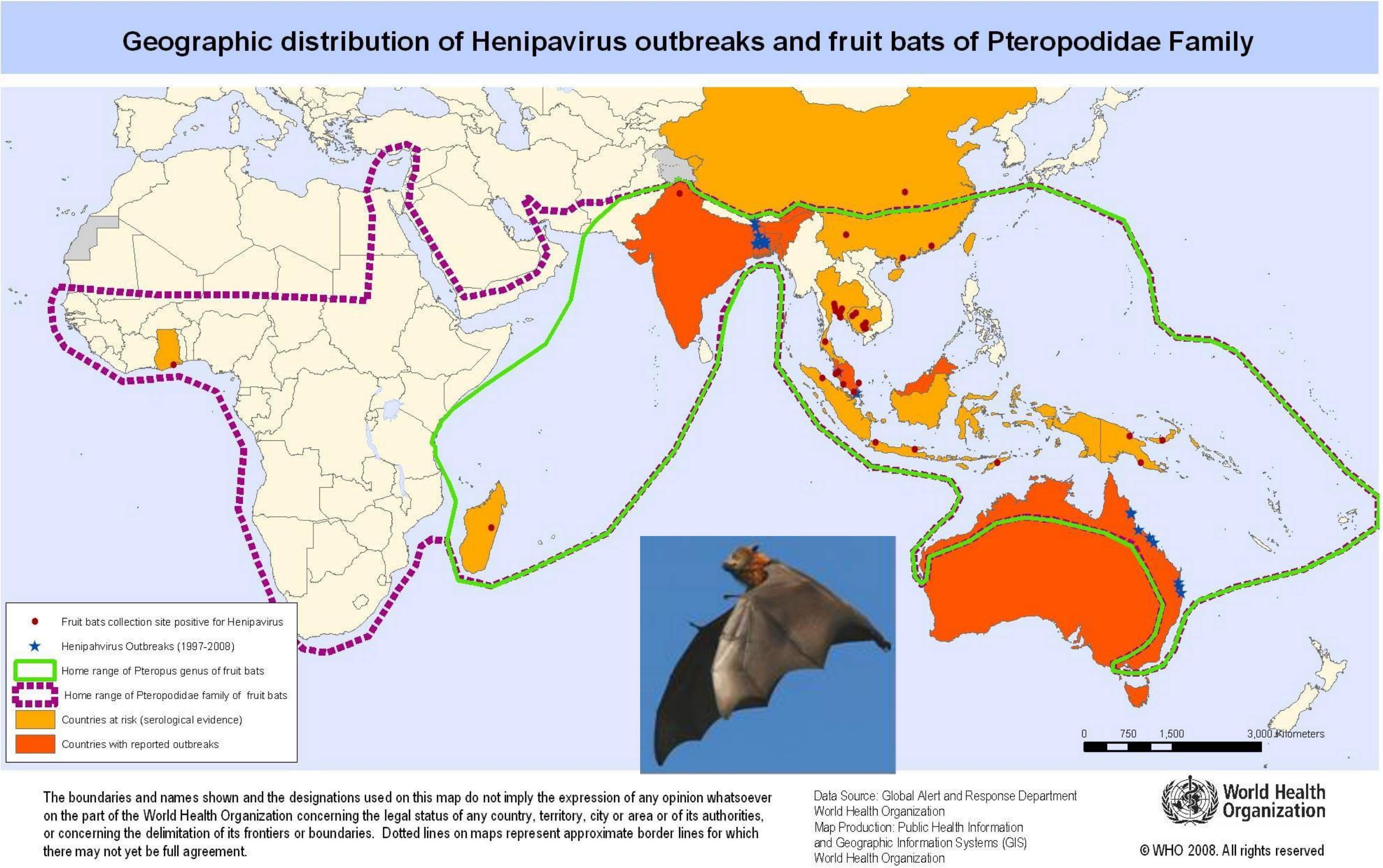


Virus Research December 2011 (162)

Nipah Virus

- RNA virus, paramyxoviruses, henipavirus
- Recent outbreaks in Malaysia and Bangladesh
- Reservoir are bats in China, SE Asia, India, Madagascar, and Ghana
- Pigs are hosts
- Humans, cats, dogs develop infection through direct contact with pig respiratory secretions and urine
- Malaysia outbreak: ? Person to person transmission
- Viral encephalitis with progression to coma, + respiratory symptoms, high mortality

Nipah Virus


Geographic distribution of Henipavirus outbreaks and fruit bats of Pteropodidae Family
Fruit bats collection site positive for Henipavirus
Henipahvirus Outbreaks (1997-2008)
Home range of Pteropus genus of fruit bats
Home range of Pteropodidae family of fruit bats
Countries at risk (serological evidence)
Countries with reported outbreaks
0 750 1,500 3,000 Kilometers
The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.
Data Source: Global Alert and Response Department
World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization
World Health Organization
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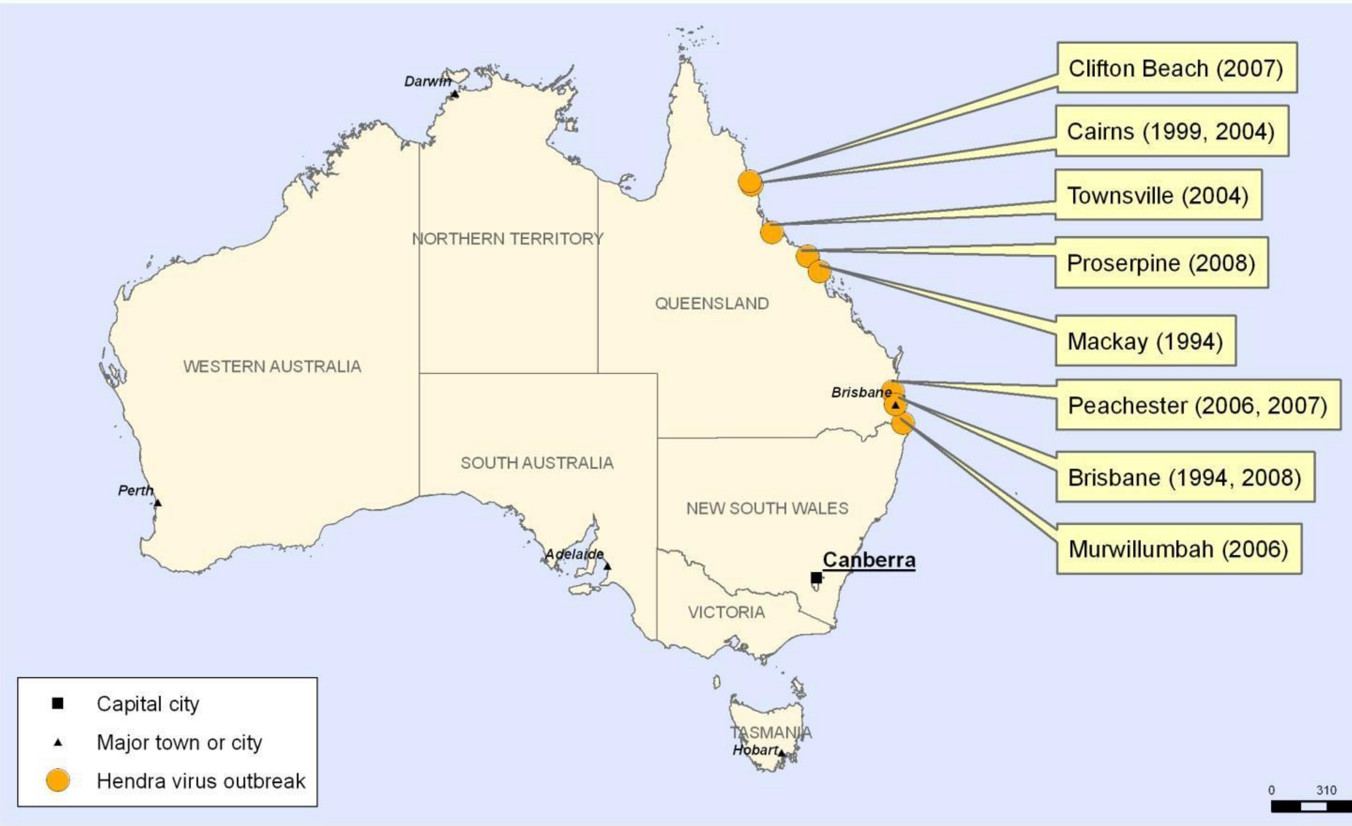
Hendra Virus

- RNA virus, paramyxoviruses, henipavirus
- Bats are the natural reservoir
- Outbreak in horses in Australia
- Four identified human cases in after close contact with horses
  - Two died
- Acute influenza-like illness, meningoencephalitis, seizures, coma

Hendra Virus

Geographic distribution of Hendra virus outbreaks in Australia from 1994 to July 2008

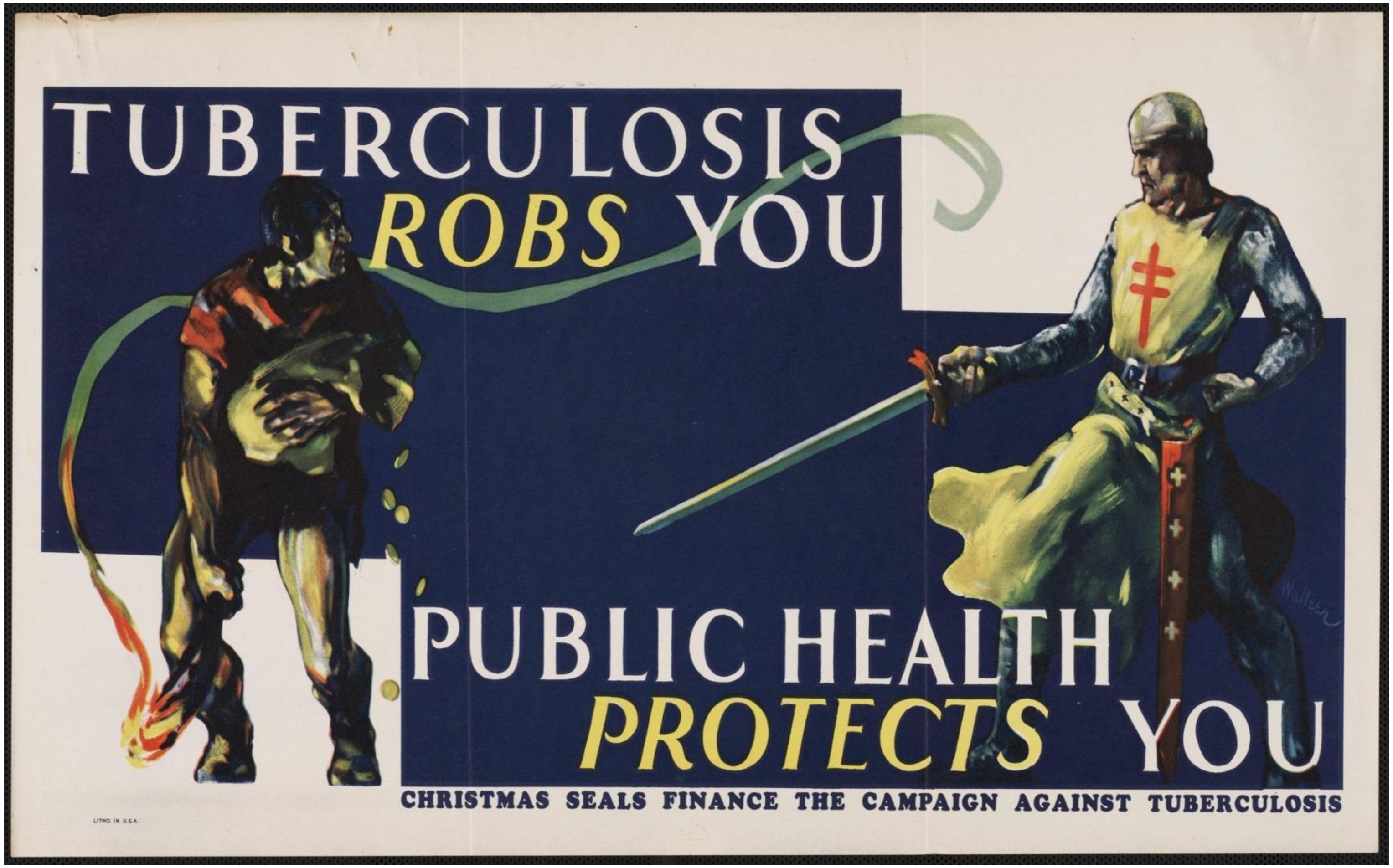


The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Public Health Information and Geographic Information Systems (GIS)
World Health Organization

World Health Organization

Tuberculosis

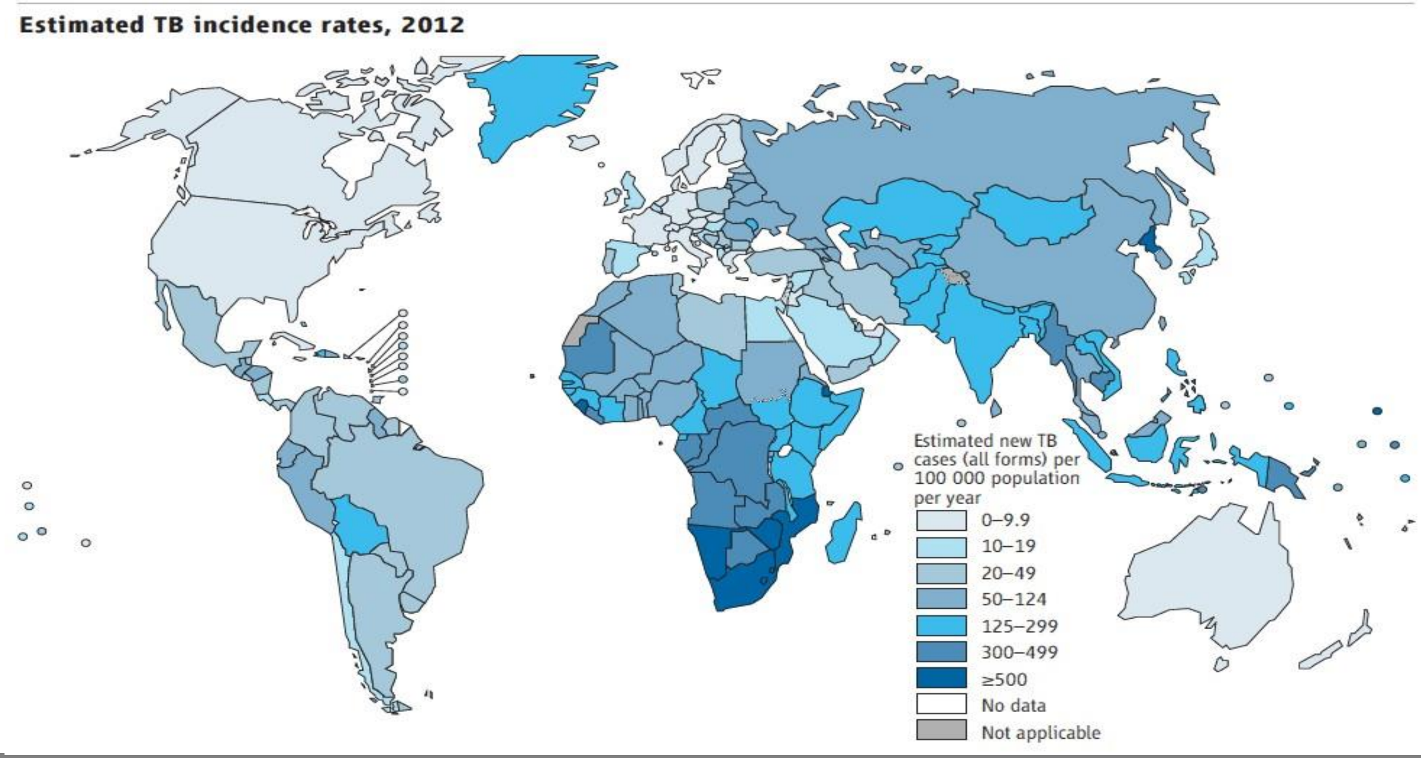


Global Burden of Tuberculosis

9.2 million cases and 1.7 million deaths yearly Associated with co-pandemic of HIV

Drug-resistance increasingly common

One third of the world's population is infected with LTBI oFocus is on identification and treatment of active TB (DOTS) oScreening for LTBI is not routinely done in most countries oIncreasing efforts to extend LTBI treatment to HIV populations



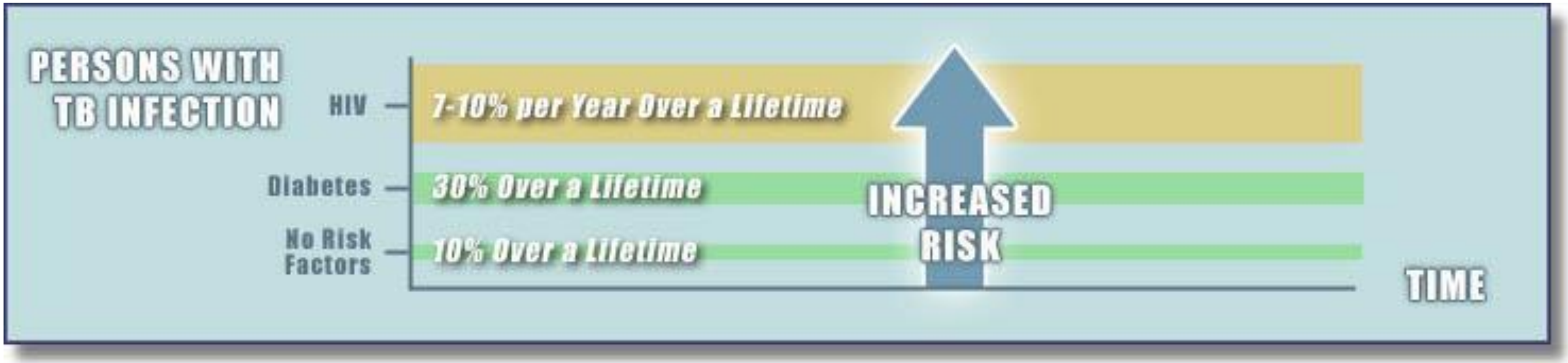
TB Pathophysiology

Spread person-to-person through the air Droplet nuclei may remain in the air Primary infection

- oInhale tubercle bacilli
- oReach alveoli, engulfed by macrophages
- oSome multiply intracellularly and released
- oImmune system (cell-mediated) prevents progression

Activation

- oTubercle bacilli overcome immune system
- o"5% risk in 2 years, 10% lifetime" (may be lower – **Am J Respir Crit Care Med 2014 NOV 1; 190: 1044**)



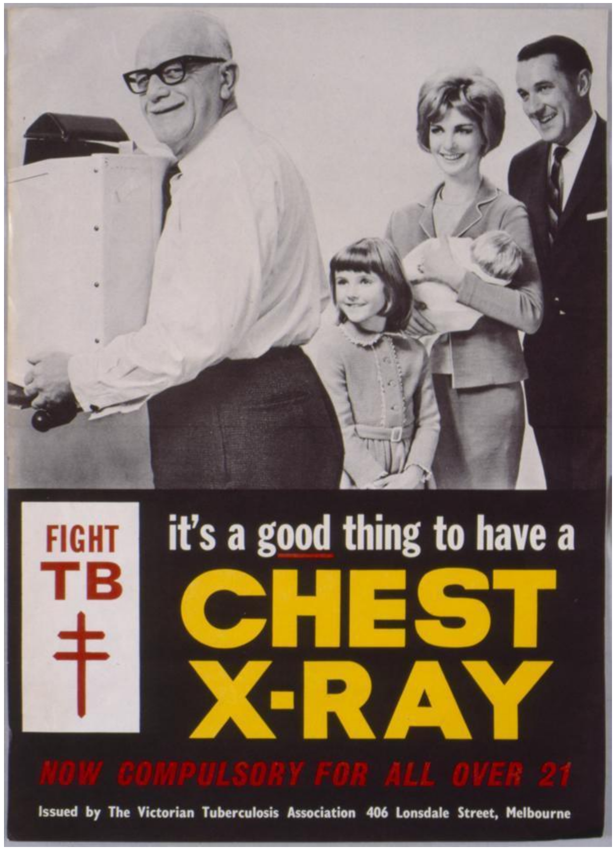
Diagnosis of TB

Clinical symptoms and signs

CXR (**not confirmatory**)

Detection of tubercle bacilli

- AFB Smear (sensitivity 50%)
- Culture and sensitivity testing
- Nucleic Acid Amplification Tests



museumvictoria.com.au

Symptoms of Active TB

- Fever
- Chronic cough
- Night sweats
- Hemoptysis
- Weight loss
- Fatigue

Active TB

Chronic infection with *Mycobacterium tuberculosis.*

Pulmonary most common (80%)

- Pulmonary and laryngeal TB are contagious

Extrapulmonary (20%)

- Lymphadenitis (scrofula)
- Skeletal
- Renal
- Meningeal

CXR

Patchy or nodular infiltrate

Apical- or subapical-posterior areas of the upper lobes or the superior segment of a lower lobe

Especially if bilateral or associated with cavity formation

AFB Smear

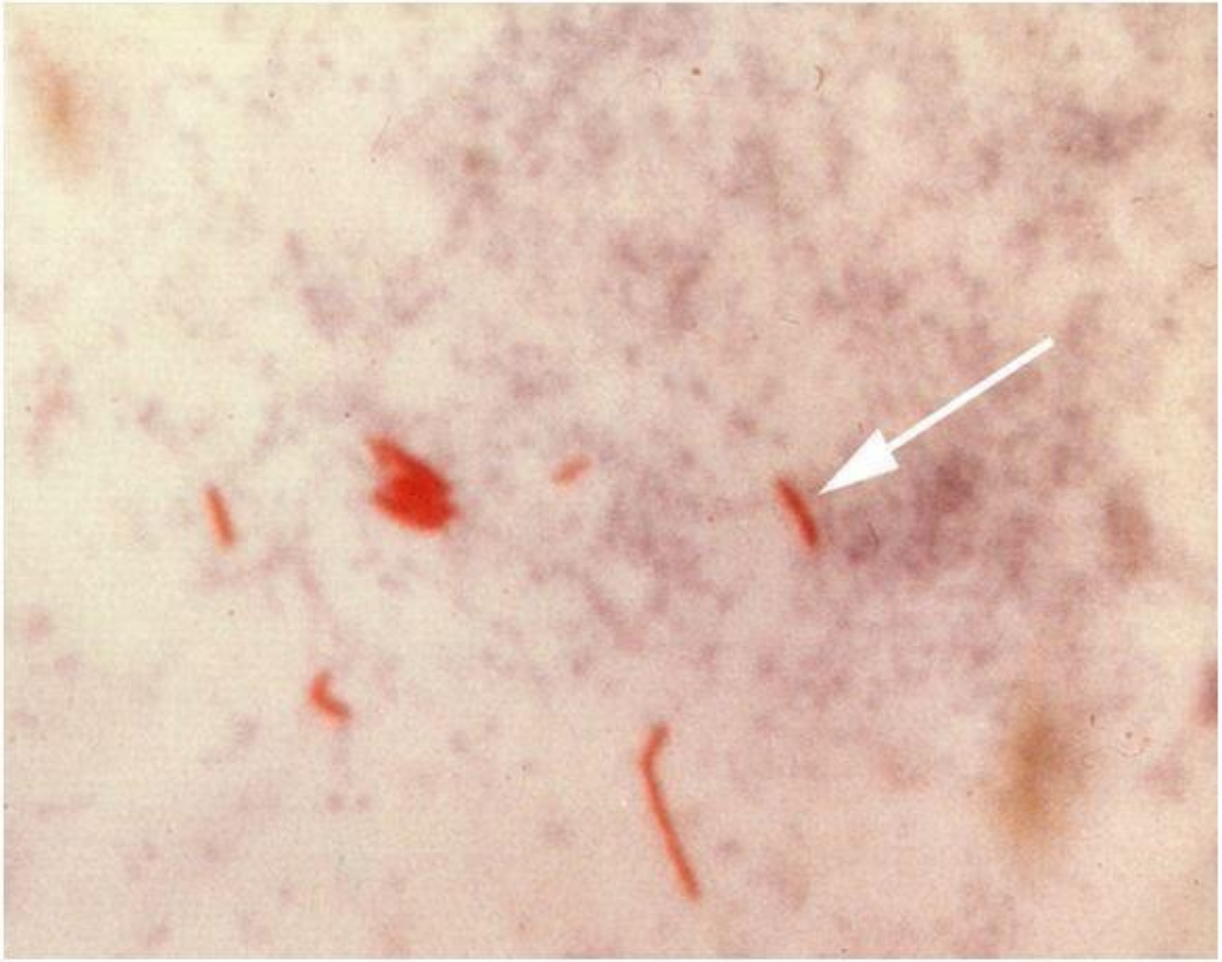


Figure 9. Sputum specimen demonstrating acid fast bacilli (AFB) (arrow). Source CDC.

Treatment of <u>ACTIVE</u> TB

"4 for 2 and 2 for 4"

INH, RIF, PYR, ETH X 2 months, **<u>then</u>**
INH, RIF X 4 months

Modify regimen if necessary after antibiotic susceptibility results are available

Check bacteriologic response monthly HIV

test

<u>"Never add a single drug to a failing regimen"</u>

INH = isoniazid
PYR = pyrimethamine

RIF = rifampin ETH
= ethambutol

Treatment of <u>ACTIVE</u> TB

4 Month Moxifloxacin based regimens for Drug-Sensitive TB

- 1931 patients randomized into 1 of 3 treatment groups (1:1:1)
  - Control group (standard RIPE therapy) – 6 months
  - “INH” arm (Moxi, INH, RIF for 4 months to include 2 months PZA)
  - “ETH” arm (Moxi, RIF for 4 months to include 2 months PZA and ETH)

- No significant safety differences
- The regimens with 4 months of moxifloxacin did **<u>NOT</u>** meet criteria for noninferiority compared to the standard of care
  - Moxi groups had a more rapid decline in bacterial load compared to standard
  - Moxi groups had more likelihood of relapse at the end of therapy

When are they non-infectious?

On adequate therapy

Clinical response

Three consecutive negative sputum smears from sputum collected on different days

Infection Control

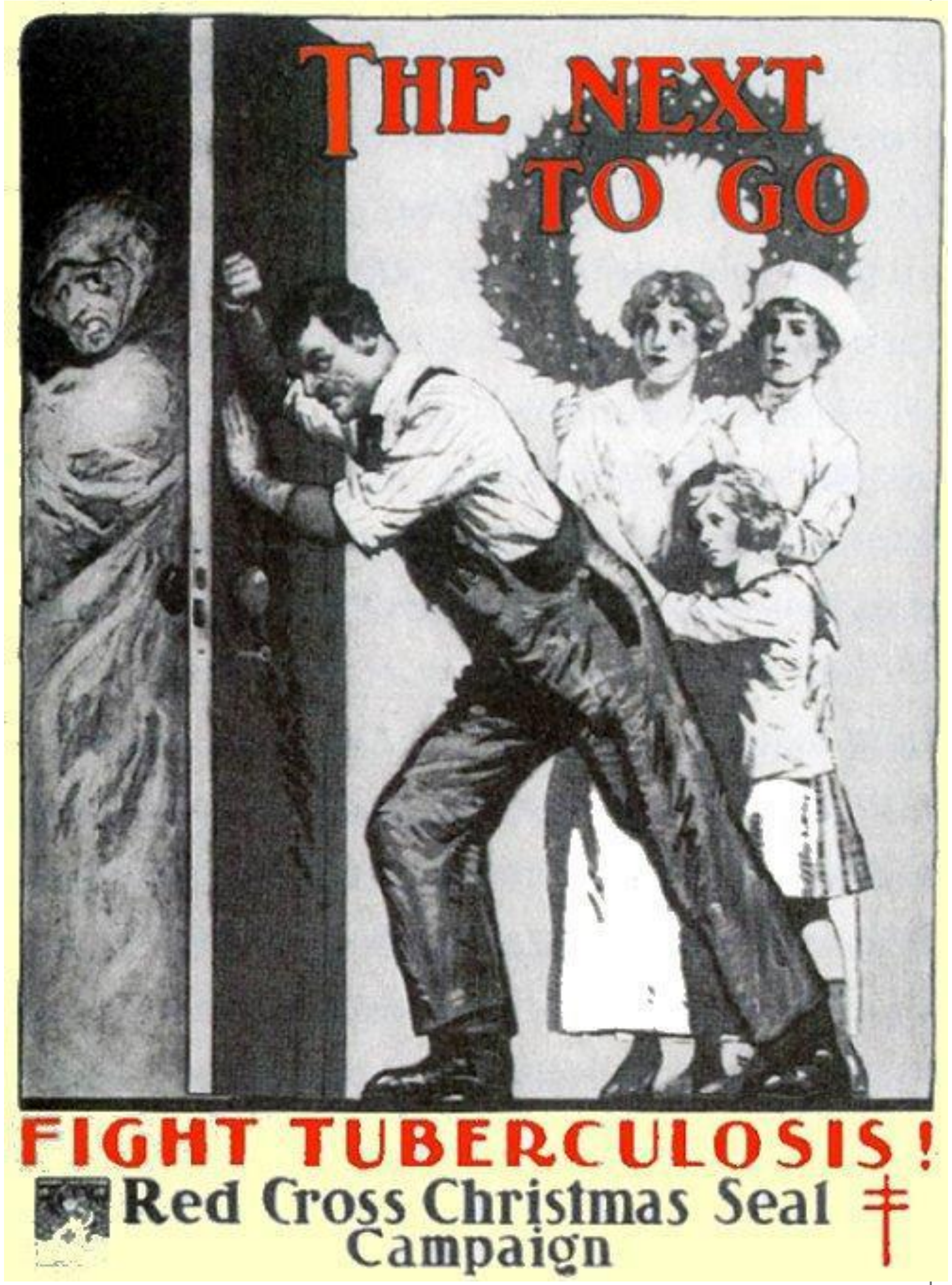
Administrative controls

- **Primary strategy for infection control!**
- "Develop policies and protocols to ensure the rapid identification, isolation, diagnostic evaluation, and treatment of persons likely to have TB"

Engineering controls (ventilation)

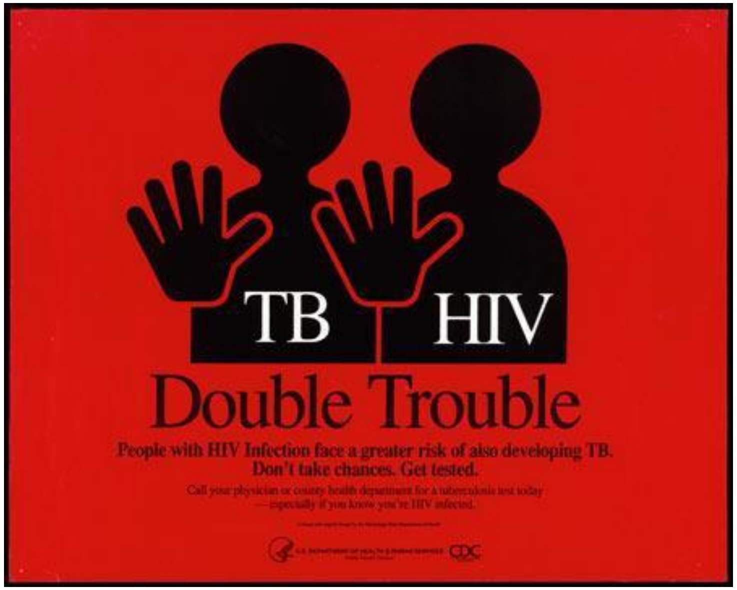
- Isolation
- Negative pressure rooms

Personal respiratory protection (N95)



HIV and TB

10% risk of progression per year Atypical presentations, anergy Leading cause of death in HIV patients MDR and XDR TB
Drug interactions
Reconstitution syndrome



apps.nlm.nih.gov

MDR = multi-drug resistant XDR = extremely drug resistant

MDR and XDR

MDR=INH and RIF resistance

XDR=MDR+

- Any fluoroquinolone; **AND**
- 1 of 3 injectable second line drugs
  - Capreomycin
  - Kanamycin
  - Amikacin

MDR = multi-drug resistant
XDR = extremely drug resistant

INH = isoniazid
RIF = rifampin

LTBI vs. Pulmonary TB Disease

LTBI

TST* or IGRA† positive

Negative chest radiograph

No symptoms or physical findings suggestive of TB disease

Active Pulmonary TB

TST or IGRA usually positive Chest

radiograph may be abnormal

Symptoms *may* include one or more of the following: fever, cough, night sweats, weight loss, fatigue, hemoptysis, decreased appetite

Respiratory specimens *may* be smear or culture positive

* Tuberculin Skin Test (TST)

† Interferon Gamma Release Assay (IGRA)

What defines a positive TB test?

a) 5 mm
b) 10 mm
c) 15 mm
d) It depends on the epidemiological characteristics and degree of TB exposure of the patient

Table 7. Criteria for tuberculin positivity, by risk group

Reaction ≥5 mm of induration	Reaction ≥10 mm of induration	Reaction ≥15 mm of induration
Human immunodeficiency virus (HIV)-positive persons	Recent immigrants (i.e., within the last 5 yr) from high prevalence countries	Persons with no risk factors for TB
Recent contacts of tuberculosis (TB) case patients	Injection drug users	
Fibrotic changes on chest radiograph consistent with prior TB	Residents and employees† of the following high-risk congregate settings: prisons and jails, nursing homes and other long-term facilities for the elderly, hospitals and other health care facilities, residential facilities for patients with acquired immunodeficiency syndrome (AIDS), and homeless shelters	
Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of ≥15 mg/d of prednisone for 1 mo or more)*	Mycobacteriology laboratory personnel	
	Persons with the following clinical conditions that place them at high risk: silicosis, diabetes mellitus, chronic renal failure, some hematologic disorders (e.g., leukemias and lymphomas), other specific malignancies (e.g., carcinoma of the head or neck and lung), weight loss of ≥10% of ideal body weight, gastrectomy, and jejunoileal bypass	
	Children younger than 4 yr of age or infants, children, and adolescents exposed to adults at high-risk	

Includes patients taking TNF-α antagonists

*Risk of TB in patients treated with corticosteroids increases with higher dose and longer duration.

† For persons who are otherwise at low risk and are tested at the start of employment, a reaction of ≥15 mm induration is considered positive.

SOURCE: Adapted from Centers for Disease Control and Prevention. Screening for tuberculosis and tuberculosis infection in high-risk populations: recommendations of the Advisory Council for the Elimination of Tuberculosis. MMWR 1995;44(No. RR-11):19–34.

CDC. *MMWR* 2000;49:1-51.
CDC. *MMWR* 2004;53:683-686.

CDC Guidelines Call for Targeted Testing Only

Targeted testing:

"…targeted tuberculin testing programs should be conducted only among groups at high risk and discouraged in those at low risk." (MMWR 2000)

All military services conduct testing at accession

CDC clearly considers high-risk:

- Hospitals and health care settings
- Prisons
- HIV-infected
- Homeless
- Contacts of active case
- ***NOT* Military**

Testing for M. tuberculosis Infection

Mantoux tuberculin skin test (TST)

Skin test that produces delayed-type hypersensitivity reaction in persons with *M. tuberculosis* infection

Interferon Gamma Release Assays (IGRAs)

Blood tests that measure and compare amount of interferon-gamma (IFN-γ) released by blood cells in response to *M. tuberculosis* antigens.

These include:

1. *Quantiferon® Gold-in-tube (QFT-GIT)*
2. *T-SPOT®.TB*

Oxford Immunotec

Harnessing the power of T cell measurement

The Tuberculin Skin Test

Cell-free purified protein fraction extracts obtained from a human strain of *M. tuberculosis*

In use for over a century

Problems with TST

- ***Positive predictive value is low if prevalence of infection is low***
- Errors and variability in administration
- False negatives and false positives

Pseudoepidemics of TST reactions reported in hospitals, prisons, reservations, military populations

Administering the TST

Inject 0.1 ml of 5 TU PPD tuberculin solution intradermally on volar surface of lower arm using a 27-gauge needle

Produces a wheal 6 to 10 mm in diameter

CDC. *MMWR* (Appendix F) 2005;54(RR-17):138-9.

Reading the TST

Measure reaction in 48 to 72 hours

Measure induration, **not erythema**

Record reaction in millimeters, not "negative" or "positive"

Ensure trained health care professional measures and interprets the TST

CDC. *MMWR* (Appendix F) 2005;54(RR-17):138-9.

Boosting and Two-Step Testing

Boosting

- May have an initially negative test due to waning responsiveness
- First test may stimulate immune response for second test
- Second test positive=boosted reaction

Two-step testing

- Done on initial test if annual testing is planned
- Prevents interpreting a subsequent annual TST as a new seroconversion
- A negative first test with a positive second test should be evaluated for LTBI.

Interferon Gamma Release Assays (IGRA)

Measures interferon-γ released from lymphocytes incubated with antigens to MTB

- *Unknown rate of progression to active TB*

- *Lack of "gold standard" for LTBI prevents defining the sensitivity and specificity of the test*

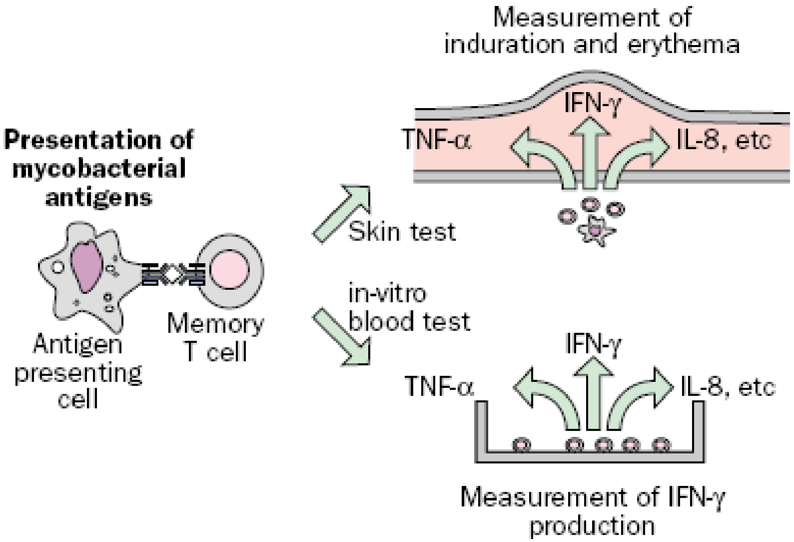


Figure 1: **In-vivo and in-vitro diagnostic tests**

Andersen P et al. *Lancet* 2000;356:1099.

When should I use the IGRA?

Depends who you talk to

- oCDC guidelines: may be used to replace TST, but don't do both oUK, many other European countries: use IGRA as confirmatory test
- oMilitary policies conform with CDC, but Navy Great Lakes was using it as a confirmatory test

Evolving issue, not resolved yet

- oMore data
- oEvolving technology

IGRA preferred among BCG vaccinated

Other LTBI Testing Issues

Must maintain good quality testing program, whether TST or IGRA

- Both are <u>difficult in the field</u>
- **<u>Should only be performed for contact investigations</u>**
- Useful QA/QC guidelines for TST quality control in Appendix F of: CDC.*MMWR* 2005;54(RR-17):138-9

<u>Tubersol® is the only TST that should be used</u>

- False positives with Aplisol®
- HA Policy 08-012 (29 Sept 08)

Decision to treat

“A decision to test is a decision to treat”

- Don’t ignore a positive test
- But be skeptical in low-risk populations (don’t test)

Must rule out active TB first

- Symptoms of active TB
- Compatible chest x-ray findings
- **If symptoms→3 sputum smear, culture, at least 1 NAAT test**

Look at criteria to determine cutoff

Assess risks & benefits for each individual patient

- Medical history (esp. liver disease, alcohol abuse)
- How recent was TB exposure?
- Pregnancy
- Allergies

Decision to treat

LTBI Treatment options:

Isoniazid x 9 months 5 mg/kg daily (max 300 mg daily)
Isoniazid x 9 months 15 mg/kg twice weekly (max 900 mg daily)

Don’t use the 6 month option if your patient can tolerate the longer option

Isoniazid 15 mg/kg (max 900 mg) + Rifapentine once weekly for x 3 months given once weekly

10.0–14.0 kg 300 mg
14.1–25.0 kg 450 mg
25.1–32.0 kg 600 mg
32.1–49.9 kg 750 mg
≥50.0 kg 900 mg maximum

Rifampin 10 mg/kg (max 600 mg) x 4 months

When dosing, round up to the nearest 50-100 mg

TREATMENT DOSE NOT ELIMINATE THE RISK OF ACTIVE DISEASE*

*Am J Respir Crit Care Med 2014; 190: 1044

Screening for LTBI in the US Military

Over 250,000 tests per year among recruits
Accessions: all services do universal screening

- oArmy (DA PAM 40-11; 20 Oct 2008)
- oNavy (BUMED Instruction 6224.8A; 12 Feb 2009)
- oAir Force (AFI 48-105; 1 Mar 2005)

Prevalence of TST reactors

- oNavy: 5%
- oArmy: 3%
- oAir Force: 1.5%
- o***Depends on proportion of foreign-born***

Deployment-related screening

What about guidelines for travelers?

US Guidelines (CDC Yellow Book): both pre- and post-travel testing for those with "prolonged exposure to tuberculosis…e.g. [routine contact with] hospital, prison, and homeless shelter populations"

IDSA Guidelines: TST "should be performed for those with anticipated exposure to TB or long-term stays in developing areas or when requested by the traveler because of concern about exposure"

TRAVAX: "travelers to countries with high risk (i.e., > 100 cases per 100,000) should have pre-departure testing if staying for > 1 month; travelers to countries with moderate risk (approximately 25-100 cases per 100,000) should have pre- departure testing if they plan on staying for > 3 months"

Canadian Guidelines: a single, post-travel test based on duration of travel as well as TB incidence in the country visited.

1. MF Iademarco. Tuberculosis. In: Health Information for International Travel 2008. Atlanta, GA: CDC, 2008. 2. Hill et al. *CID* 2006;43:1514.

3. Shoreland. Tuberculosis. Available at www.travax.com ; Accessed 6 June 2009.
4. W Wobeser et al. Surveillance and screening in tuberculosis control. In: Canadian tuberculosis standards: Public Health Agency of Canada, 2007.

What does the US military for deployers?

Air Force

Targeted testing after deployment since '05 (AFI 48-105)

Navy

Used to test operational units yearly with TST

Now targets testing during PHA with questionnaire (BUMEDINST 6224.8A, 12 Feb 2009)

Army

Used to test before deployment, after deployment, and then again 3-6 months after deployment (3 tests per deployment)

In 2008, moved to targeted testing after deployment using DD 2796 (OTSG Memo, 25 Sept 2008)

Testing **SHOULD NOT** be routinely performed during deployment

See http://www.pdhealth.mil/tuberculosis.asp

Recent Deployment TB Epidemiology

Outbreaks on Navy ships—common in the 1960s

- USS Wasp (1998): 21 infected from failure to diagnose index case
- USS Ronald Reagan (2003): 1 reactivation despite prior INH Rx

Active TB: **lower rate of disease than in the US population**

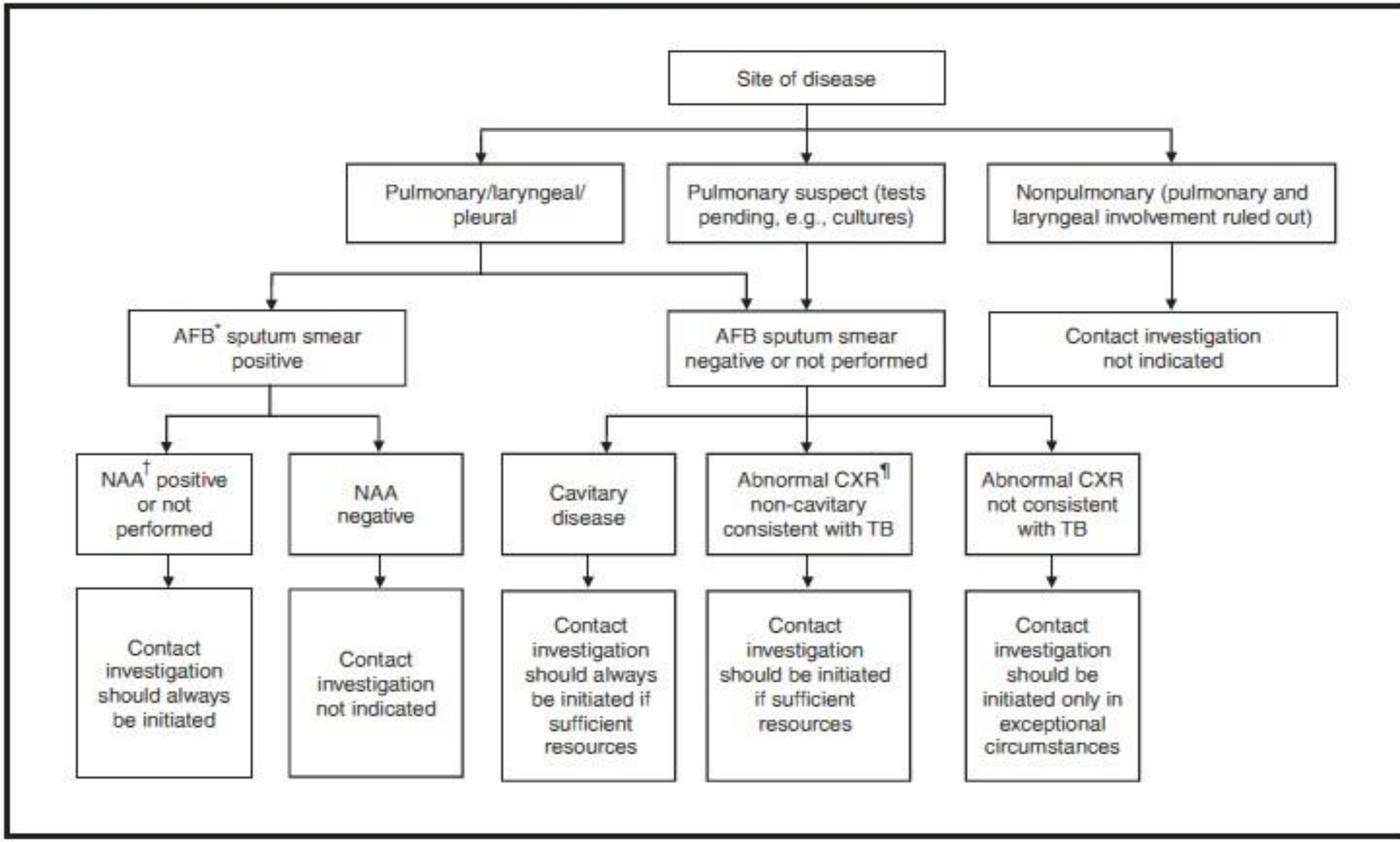
TST reactors during deployment

- Prevalence of TST conversion: 1-2% without specific exposure history (similar to prevalence in recruits)
- Numerous false positives and pseudo-outbreaks reported

Lamar. *Mil Med* 2003; 168(7):523-7.
CDC. *MMWR*. 2007;55:1381-2.
Camarca MM and Krauss MR. *Mil Med* 2001;166(5):452-6
Mancuso J. *AJRCCM* 2008:177:1285-9.

Managing TB Exposure in a Deployed Setting

FIGURE 1. Decision to initiate a tuberculosis (TB) contact investigation



* Acid-fast bacilli.
† Nucleic acid assay.
§ According to CDC guidelines.
¶ Chest radiograph.

Managing TB Exposure in a Deployed Setting

Document TB symptoms (or the lack thereof)

High or medium priority contacts should receive TST at initial encounter

All contacts should have a TST at 8-10 weeks post-exposure A

diameter >5 mm is positive for any contact

Any contact with TB symptoms should be managed immediately regardless of skin test results

Other important management issues

Directly observed therapy (DOT)

- Standard of care for **<u>Active</u>** TB
- May be used for LTBI, but uncommon
- **<u>Refer to Preventive Medicine</u>**

Disease reporting

- **<u>Active TB is a reportable disease</u>**, LTBI is not
- Positive TST or IGRA must be documented in an electronic registry (ALTHA, MEDPROS, etc)
- Reportable diseases are reported to Preventive Medicine both in garrison and on deployment

TB Summary

Remember for TB testing, **a decision to test is a decision to treat**

LTBI is **not symptomatic** and has **normal Chest X-ray**

Targeted testing for TB with skin test or IGRA (“TB blood test”) Measure

the **swelling**, *not the redness* on a TB skin test

Consider **IGRA for foreign born** individual who may have receive BCG as child

Always **rule out** active TB before treating for LTBI Active TB

requires **airborne isolation** when possible **Report** active TB

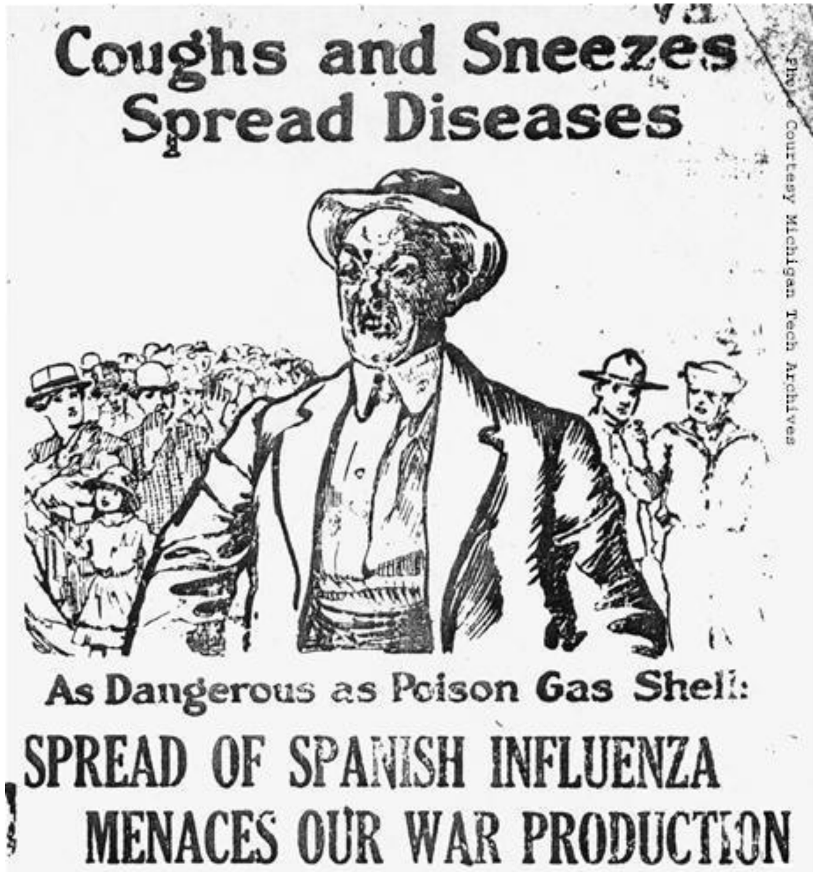
cases to preventive medicine

Directly observed minimum 4 drug therapy for active TB

General Respiratory Summary

- Virus are constantly evolving and novel highly virulent respiratory viruses WILL circulate in the future
- An influenza strain that is highly transmissible (e.g. H1N1) AND highly virluent (e.g. H5N1) will likely result in high mortality
- Get vaccinated, some protection even when mismatches occur
- Maximize good hand hygiene, distance from others, and personal protective measures
- Consider isolation of patients and assume worst case initially
- Use common sense and avoid contact with animals, local markets, and areas with known outbreaks of respiratory infections

Thank You
Questions?



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